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MUHC -Technology Assessment Unit

The Use of Biventricular Pacemakers at the McGill University Health Centre

A Technology Assessment

by

The Technology Assessment Unit (TAU)

of the McGill University Health Centre

(MUHC)

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Invitation. This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it, preferably with acknowledgment. More important, to assist us in making our own evaluation, it would be *deeply appreciated* if potential users could inform us whether it has influenced policy decisions in any way, and even if it has not, whether it has been helpful in informing decision makers.

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Executive Summary

In addition to high mortality, congestive heart failure is characterized by high morbidity, repeated hospitalizations, and reduced exercise tolerance. Several pharmacologic and non-pharmacologic interventions have been shown to reduce both mortality and morbidity. A recent technologic intervention is biventricular pacing, also known as cardiac resynchronization therapy (CRT). The rationale of this approach is to diminish ventricular asynchrony and thus improve ventricular function in those cases in which intraventricular conduction is prolonged.

Several randomized studies have been performed. No study has demonstrated improved survival with isolated CRT or CRT combined with an implantable cardiac defibrillator (ICD) versus CRT. The studies suggest improvements in the patients' quality of life, but there was no consistent evidence of reduced hospitalizations with biventricular pacing with or without ICD compared to ICDs. Approximately 10% of installations can't be successfully completed.

The cost of implantation of the CRT-ICD is $34,677 per patient, compared to $24,704 for an ICD alone. In terms of opportunity costs given the fixed budget of the cardiology (pacemaker) department, this additional expense means that for every 2 combined CRT-ICD devices installed, there will be a budget reduction corresponding approximately to 1 fewer ICD being available. While CRTs have no demonstrated mortality benefit, ICDs have been shown to improve survival in very similar patients. If there were 6 combined CRT-ICD installations over the next 12 months, the additional $60,000 would likely have to be offset by the installation of 3 fewer ICD devices.

Based on the lack of clinically meaningful differences consistently identified to date, including the difficulty in predicting responders, the current state of clinical equipoise and the consequent existence of ongoing research projects, the difficulties in installation and the increased costs, TAU does not at this time recommend the routine approval of combined CRT/ICD technology at the MUHC. Despite this recommendation, it should not be concluded that there is no role for this technology at the MUHC as TAU firmly encourages

the participation of the MUHC in the Canadian Institute of Health Research funded Raft trial to further clarify the risks and benefits of this therapy.

TAU recognizes that unique cases may arise whereby there is a strong clinical suspicion that a patient, ineligible for the current research project, may be thought to greatly benefit from this technology. For these exceptions, the evidence cited in this present document, which summarizes which patients are most likely to obtain maximum benefit, will be useful. A decision to initiate the CRT-ICD therapy in these exceptional cases should only be made after formal approval by a committee of the Division of Cardiology.

Recommendations:

Based on the lack of mortality benefits, the marginal impact on quality of life, the lack of long term results at this time, the presence of ongoing research designed to establish the benefit of this therapy, and the considerable opportunity costs, the TAU does not recommend routine use of biventricular pacemakers with ICD at the MUHC.

TAU encourages the active participation of the MUHC in the CIHR funded trial that is further examining this technology. At present, TAU does not expect annually that more than a maximum of 5 or 6 exceptional cases would require biventricular pacing outside the context of the funded research trial.

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1. Introduction

The clinical syndrome of congestive heart failure (CHF) is the final pathway for several cardiovascular diseases[1]. The incidence and prevalence of heart failure have been constantly increasing due to the aging of the population, and improved survival from CHF and other cardiovascular diseases, such as hypertension and coronary disease[2].

The 5-year mortality in patients with heart failure estimated outside of clinical trials is approximately 50 – 60%[2]. The annual mortality is estimated to be approximately 5-15% in patients with NYHA class II, 20-50% in patients with NYHA class III, and higher than 50% in patients with NYHA class IV[3]. Mortality within clinical trials has generally been less than that observed in population studies, due to the selection bias in recruiting younger, and healthier patients.

In addition, heart failure is one of the diagnoses with the highest rate of hospitalizations, resulting in high costs to society[4]. Heart failure treatment represents 1-2% of the health care expenditures in developed countries[5], with 75% being spent on hospitalizations[2]. It is the 5th most common cause of hospitalization in the general population, and the most common cause of hospitalization in the elderly[5]. In Canada, 45,629 patients were hospitalized with a main diagnosis of heart failure, accounting for 447,830 days in-hospital, with a 20% chance of being re-hospitalized within one year[6]. In Quebec, there were over 13,000 admissions in 2000, and more than 300 annually at the MUHC. The mean length of stay at the MUHC was 11.7 (SD 13) days.

Use of ACE inhibitors, beta-blockers, and spironolactone in patients with heart failure has resulted in a decrease in both morbidity and mortality, and should be universally applied. Other treatments that may improve outcomes may include dual chamber pacing, implantable cardiac defibrillator (ICD) and, in refractory cases, left ventricular assist devices and cardiac transplantation. Patients with CHF often have ventricular conduction delays that can prolong the ejection time, reduce ventricular ejection fraction, and increase mitral regurgitation, and are associated with a worse prognosis[4]. Biventricular pacing, otherwise known as cardiac

resynchronization (CRT) was first described in 1994[7,8], as a means of correcting these abnormalities.

The biventricular pacemaker is the size of a typical pacemaker, and requires 3 leads (one for the right atrium, either a standard transvenous pacing lead or a transvenous defibrillation lead for the right ventricle, and a left ventricle lead, inserted into a cardiac vein via the coronary sinus)[9]. The devices are presently approved by regulatory agencies for NYHA functional class III or IV patients who remain symptomatic after treatment with optimal medical therapy, and have a left ventricular ejection fraction of less than 35%, and QRS duration longer than 130 ms.[5]

2. Literature Review

2.1 Method

The literature search was performed by using the Medline, Pubmed, Cochrane, and health technology agencies databases. Websites that provide results and information on clinical trials were also searched. A list of these health technology agencies databases and sites with randomized studies' results is provided in Appendix 1.

Search terms included: biventricular pacing, biventricular pacemakers, resynchronization, resynchronisation, pacing (and heart failure). No restriction for dates of publication was made for the database searches. No language restriction was applied at first, but only articles in English, French, German, Italian, Spanish and Portuguese were reviewed for relevance.

3. Results

We were unable to identify any published technology assessments of biventricular pacemakers. We did identify clinical practice guidelines endorsed by The American College of Cardiology (ACC) and the American Heart Association (AHA)[10]. These guidelines are written by experts and are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure and provide clinical guidance. However as these guidelines do not explicitly consider cost-effectiveness and often present a uniquely American clinical healthcare perspective, they are most useful in their

summary of the efficacy of published evidence and not as formal technology assessment documents. The rapid evolution of this technology is witnessed by the ACC/AHA 2002[10] recommendation for biventricular pacing in selected patients with heart failure being listed as Class IIa (weight of evidence/opinion is in favor of usefulness/efficacy, see appendix 12), whereas in the ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in adults, published in 2001[11] this technology is cited only as an investigational procedure.

The 2002/2003 Canadian Cardiovascular Society Consensus for the diagnosis and management of heart failure also recommends that patients with heart failure who are still severely symptomatic despite optimal medical therapy, but have reasonable rehabilitation potential, with mean QRS duration > 130 ms and left ventricular ejection fraction (LVEF) < 35% **may be considered** for evaluation of resynchronization therapy for symptomatic improvement[12]. The guidelines also recommend that better candidates for this intervention may be patients with marked LV chamber enlargement (LV end-diastolic diameter > 55 mm), mitral regurgitation, very prolonged QRS duration (>150 ms), and patients with severe symptoms or high diuretic requirements[12]. The literature supporting this recommendation is thoroughly reviewed in this document.

Seven randomized trials[13 14 15 16 17 18 19] and 1 meta-analysis[20] were identified. Nine non-randomized studies were also found in the literature[2 21 22 23 24 25 26 27 28]. Patients in the published comparative studies were generally considered to be receiving optimal pharmacological therapy regardless of the treatment arm they were assigned to, although the use of beta-blockers, diuretics as needed, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, spironolactone, or digoxin was not always universal. One of these studies[13] is expected to be published in a peer-reviewed journal. Preliminary information from this study available from cardiovascular conferences was used in our report, although results that have not yet been peer-reviewed should be interpreted with caution. Among the randomized trials, with the exception of the Companion trial[13], which was open label, the Higgins trial[19], where it was unspecified and the Mustic trials[15 16 17],

which were single-blinded, all other trials were double-blinded[14 18]. A description of the published studies used in this report is provided in Appendix 2.

The interpretation of the evidence is complicated by different study designs, i.e., non-randomized, randomized crossover, and randomized parallel studies. Also, the comparative groups have not been constant. Biventricular pacing has been compared to no pacing, regular right ventricular pacing, and the combination of biventricular pacing with ICD. In this review, conclusions will be drawn from the randomized studies, although data from non-randomized studies are also presented in the appendices. The inclusion and exclusion criteria, length of follow-up, and outcomes of the different studies are given in the appendix 3. There were 4 trials of biventricular pacing without ICD compared with either no pacing or right-ventricular pacing [14 15 16 17]. There were 2 trials of biventricular pacing with ICD comparing with ICD alone[18 19]. Another trial compared both biventricular pacing with and without ICD to no pacing[13]. Two randomized studies were not included due to short follow-up period, small sample size (13 and 42 patients), and unusual design[29 30].

In general, only CHF patients with NYHA III-IV, ejection fraction < 35%, and QRS > 130 ms, or QRS > 120 ms and PR interval > 150 were included in the trials. In some of these trials, approximately 15%-20% of the patients enrolled were not randomized, either due to unsuccessful device implantation, 8%-12%, or deaths, up to 4%[31 32 14,18], possibly resulting in selection bias. In addition, it was not clear if the deaths occurred due to the progression of the disease or if it was related to the device or its implantation procedure. Recognized contraindications to biventricular pacing include the presence or likelihood of competitive or intrinsic rhythms, pre-existing ICD, as it may cause unwanted delivery, or inhibition of the therapy provided by these devices, incessant arrhythmias, and coronary venous vasculature that is inadequate for lead placement, as indicated in a venogram[9].

Only one trial has examined 263 patients in NYHA I/II and found no improvements in health outcomes including quality of life measures[19].

Most studies were designed to examine quality of life measurements as the principal endpoint. Mortality and repeat hospitalizations were considered as secondary outcomes. The quality of life measurements were generally evaluated as the changes in NYHA classification, the 6-minute walk test (6MWT), and the Minnesota Living with Heart Failure questionnaire (LHFQ). The LHFQ assesses the patients' perception of how their emotional and physical state is impaired by heart failure, with higher scores representing a more severe impairment[33]. The lack of precision and reliability of the NYHA scale in distinguishing differences of 1 grade is well recognized[34]. There is a better reproducibility with the 6MWT and the LHFQ scales, but the clinical significance of these scales with regards to daily living activities is hard to fully interpret. Other measurements include the VO2 max, and maximal treadmill effort, but again, the translation of improvements in these parameters to direct benefit in daily quality of life is difficult. Appendix 4 has more detailed information about the validity, and reliability of these scales. Detailed results are shown in appendices 5-9.

3.1 Mortality

Biventricular pacing vs no pacing

The 1-year all-cause mortality seen in observational studies using biventricular pacing ranged between 3.5% and 20%[2 21 27]. This immense variability, coupled with a lack of a reliable comparator illustrates the impossibility in relying on observational data to make sensible decisions for the use of this technology.

Pooling the results of the Miracle and Companion randomized trials did not reveal differences in all-cause mortality after 6 months between patients using biventricular pacing and no pacing, OR 0.91 (0.61 , 1.34) [14 13,35].

Biventricular pacing +ICD vs no pacing

The Companion results showed a 36% reduction (HR:0.64 / 95% CI: 0.48 , 0.86) in mortality at 1 year with CRT-ICD compared to patients with no pacing[13,35]. Many deaths in studies with biventricular pacing without ICD were arrhythmic, stressing the importance of combining an ICD with biventricular pacing in these high risk patients[3 7]

[24]. It is impossible to attribute a benefit to biventricular pacing in studies comparing biventricular pacing with ICD with no pacing, since treated patients also received ICDs which are known to be associated with better survival.

Biventricular pacing + ICD vs Biventricular pacing

A non-randomized patient series (n=135) showed a 24% (HR: 0.76 / 95% CI: 0.56 , 0.96) reduction in all-cause mortality, and a 92% (HR:0.08 / 95% CI: 0.05 , 0.42) reduction in sudden death at 1 year in patients using biventricular pacing with an ICD compared to biventricular pacing alone[28]. The non-randomized study design, with the combined device being used exclusively later on in the study, and the fact that the comparison is really ICD versus no ICD renders this study non-pertinent for our purposes.

Biventricular pacing with an ICD vs ICD

The results suggest similar all-cause mortality at 6 months (OR 0.78 (0.45 , 1.35) in patients using biventricular pacing with ICD comparing with patients using an ICD alone[18 19].

Biventricular pacing versus right ventricular pacing in patients with atrial fibrillation

There is insufficient data on patients with atrial fibrillation to formulate any conclusions about a possible mortality benefit[17].

Comment

The trials comparing biventricular pacing + ICD to ICD alone are the most pertinent as they offer state of the art therapy (ICD) to these high-risk heart failure patients. Despite a total of 859 randomized patients, the trials are underpowered to conclude if any meaningful difference in short term mortality is present. Moreover, the literature also lacks long-term survival data. Although it is theoretically possible that, as with other positive inotropic agents, that biventricular pacing may result in higher mortality[21], this seems unlikely as cardiac oxygen consumption is not enhanced[21]. Furthermore, there are advantages resulting from an improved systolic function, and decreased mitral regurgitation might theoretically be expected to reduce mortality[21].

3.2 Re-Hospitalizations

Biventricular pacing vs no pacing (sinus rhythm)

The pooled results of the Mustic and Miracle studies indicate a 57% reduction in heart failure hospitalizations after 6 months of follow-up in patients using biventricular pacing compared to no pacing (OR 0.43 / 95% CI: 0.25 , 0.75)[14 15].

Biventricular pacing versus right ventricular pacing in patients with atrial fibrillation

According to the Mustic trial, patients using biventricular pacing had a lower rate of heart failure hospitalizations compared with patients using right ventricular pacing alone, i.e., 7% versus 23% of patients respectively, yielding an OR of 0.25 (0.06 , 0.97) during the 6 months after the implantation[17]. The number of all cause hospital admissions was not recorded[17]. However, 27 (42%) of patients withdrew before completing this study, 7 due to the technical difficulties of left ventricular pacing[17]. The authors also concluded that there was a potential deleterious effect of right ventricular pacing, which they probably underestimated when designing the study protocol[17]. These factors and the small number of patients limit conclusions in this group of patients with atrial fibrillation[17]. After a 12-month follow-up period, Linde et al. found that the hospitalization rate in the right ventricular pacing group was 3.5 times higher than in the biventricular pacing group, i.e., 0.14 and 0.04 hospitalizations per month respectively[16].

Biventricular pacing + ICD vs no pacing

The Companion study showed a reduction in the composite endpoint of heart failure hospitalizations and death in patients using biventricular pacing with ICD, 56%, compared to no pacing, 68% (p=0.007)[35].

Biventricular pacing+ ICD vs ICD

The pooled results of the CRT-ICD vs. ICD trials suggested that heart failure hospitalizations at 6 months are similar between patients using biventricular pacing with ICD and patients using an ordinary ICD, i.e., and OR 0.89 (95%CI: 0.62 , 1.28)[18 19]. The Miracle ICD trial also suggest that the rate of all-cause hospitalizations is similar between

the two groups, OR 0.98 (95% CI: 0.64 , 1.48)[18] (calculated by subtracting the number of deaths from the number composite endpoints of death or all-cause hospitalization) .

Hospitalizations from non-randomized studies

Non-randomized studies have shown a generally a larger decrease in heart failure hospitalizations compared to the randomized studies[23] [21]. Interpretation of the non-randomized data should be evaluated with caution.

Comments

The hospitalization for the implantation of the device has not been included in the analyses of any of the randomized or non-randomized studies. Therefore, although some results suggest that biventricular pacing may decrease the need for subsequent hospitalizations, these studies overestimated its effect by ignoring the hospitalization for the implantation of the device. The impact of biventricular pacing on re-hospitalizations has not been evaluated for periods longer than 6 months.

3.3 Other Outcomes

NYHA Functional Class

Biventricular pacing vs no pacing

In the Miracle study, 68% of the patients using biventricular pacemakers had an improvement of at least 1 class after 6 months of follow-up, compared to 38% in patients with no pacing[14].

Biventricular pacing with ICD vs no pacing

No results were reported on NYHA functional class for this comparison.

Biventricular pacing with ICD vs ICD

By pooling the results of the Higgins et al., and Miracle ICD studies in patients with NYHA classes III and IV, we have found that 67% of the patients using biventricular pacing with ICD had an improvement of at least 1 point in the NYHA functional class after 6 months of follow-up, compared to 52% of the patients with no ICD alone [18] [19].

However, considering the patients with NYHA classes I-IV, the Higgins study[19] did not show any difference in the number of patients improving their NYHA classification in the Biv+ICD group compared to ICD alone.

Non-randomized studies

Non-randomized studies in patients using biventricular pacing found a larger mean improvement than the randomized studies in the NYHA functional class after 6-12 months of follow-up compared to baseline[2 21 23 24].

Quality of Life

In general, the various studies have consistently demonstrated a larger improvement in the LHFQ scale with an approximate 17 point decrease with biventricular pacing with or without the ICD, compared to 9 points with the diverse control groups[14 15 16 17 19]. Again, considering the patients with NYHA classes I-IV, the Higgins study[19] did not show any statistical difference in the improvement in quality of life in the CRT-ICD group compared to ICD alone. This may be explained by the number of minimally symptomatic patients as the subgroup of patients with NYHA III/IV did show a 16 point decrease with biventricular+ICD compared to a 5 point decrease in ICD alone ($p=0.017$)[19].

6-minute walk test

The randomized trials have demonstrated an approximate average improvement of 52 meters in the biventricular pacing group with or without ICD, compared to 34 meters with the control groups[14 15 16 17 18] in patients with NYHA classes III-IV. A similar difference was again seen in the Higgins study[19] in patients with NYHA classes I-IV. It should be noted that patients experiencing these benefits all had walked at least 250 meters in the baseline 6MWT[14 15 16 17 18]. The frequent occurrence of increased benefits in non-experimental studies has been observed, with improvements that ranged from 75 to 136 meters in these studies[21 24 26 27].

Cardiac Transplantation

A post hoc analysis of 34 patients already included in various clinical trials discussed above, and listed for heart transplantation showed that, after 6 months of biventricular pacing, 82% of the patients were in NYHA classes I or II and were therefore withdrawn from the transplant list[36]. Given the costs of complications of heart transplantation, as well as the shortage of heart donors[36], any delay in the need for a heart transplant may bring benefits to the patients and the health care system. This small post hoc analysis obviously requires confirmation in larger studies.

3.4 Safety

The list of complications observed in the published studies and their rates of occurrences based on a 3-6 months follow-up are presented in Appendix 10.

The Companion trial reported a 0.3% rate of deaths related to the implantation procedure[37]. Some studies report the occurrence of deaths, approximately 4%, between the implantation procedure and the randomization into the study, with no specification of the cause[18 32 31]. The Higgins' study had 2 (0.4%) immediate post-operative deaths[19].

The most common complications that occurred during the implantation procedures were: left ventricular lead dislodgement (5%), coronary sinus dissection (3%), or perforation (2.3%), exit block (7.3%), and elevated pacing thresholds (3.9%)[32 31 38 18 26 15 24 39 2 40]. After the implantation procedure, the most common complications were arrhythmias (18.1%), worsening of heart failure (16.2%), hypotension (15.2%), lead dislodgement (11.1%), infection of the device or lead (1.4%), and loss of biventricular pacing capture (2.6%)[2 15 32 18 24 26 31 38 39 40].

3.5 Unsuccessful implantations

Implantation of the biventricular pacemaker was unsuccessful in 8-12% of the patients[14 15 17 18 32] was again observed in the Higgins' study where 66 of 581 (11.3%) originally planned procedures were abandoned because of inability to place the LV lead[19]. The reasons for unsuccessful implantation included inability to catheterize the coronary sinus, inability to advance the lead to its final venous destination, unstable lead

position, and unacceptably high pacing threshold[24]. According to Dr. Tom Hadjis, MD, a MUHC cardiologist and electrophysiologist, the success rate in the MUHC is approximately 82% after a learning period, during which the success rate was approximately 40%.

According to the Higgins' study even in patients with a "successful" implantation only 54% of transvenous installations had an optimal left lateral position[19].

3.6 Cost-analyses

We assumed a patient population similar to that of the clinical trials, i.e., patients with heart failure (NYHA functional class III-IV, LVEF < 35%, QRS > 130 ms). It is likely that patients will receive an ICD with their biventricular pacemaker, therefore, for our cost analysis, we included only the comparison of biventricular pacemakers with ICD to ICD alone.

Only procedure's costs are used in the cost calculation (without physicians' costs), given in Canadian dollars. Costs have been increased to account for unsuccessful implantations (10%), and lead dislodgement (5%). Based on the literature review, we have assumed that both all-cause mortality and the rate of heart failure hospitalizations are not different between biventricular pacing with ICD and ICDs[18 32] Due to the lack of follow-up information with biventricular pacing, it is assumed that no differences occur beyond 6-12 months.

The cost of a biventricular pacemaker with ICD is $31,100, which includes $24,000 for the biventricular pacemaker with ICD mechanism, $3,000 for the two right ventricular leads, $2,900 for the left ventricular lead, and $1,200 for the guide wires (source Christiane Berube – manager, Cardiology Department). A biventricular pacemaker without the ICD costs approximately $11,500 including the device, two right leads, and one left ventricular lead (sales department of Medtronic). The biventricular pacemakers last for 6-7 years[9].

Re-hospitalizations and follow-up costs

Table 1 describes the costs used in the cost calculation. The cost of the implantation of an ICD at the MUHC is $24,704 (materials, hospital and non MD professional fees, and the cost of post-procedural complications at the MUHC is $435 (http://upload.mcgill.ca/tau/icd.pdf). As we have assumed that the rate of hospitalizations and patient follow-up costs would be the same in both patients using biventricular pacing with ICD, and ICDs alone, these costs were not included in the analysis.

Table 1 - First-year costs per patient with biventricular pacing with ICD and ordinary ICDs

Resource / Cost	Cost with biventricular pacemakers-ICD (See Appendix 11 for details)	Cost with ICDs
Device and implantation costs	**$ 34,677**	**$24,704**
Cost of treatment of complications after the implantation procedure (to be applied the number of patients alive at mid-year)	**$ 987**	**$435**

Total Cost for the MUHC

Assuming 10 implants annually, an additional cost of $ 104,422 for the first year is required compared to isolated ICDs implants. If 50 patients receive a biventricular pacemaker with ICD, the additional cost will be $522,110. Since virtually all ICD candidates are also potential biventricular pacemaker recipients, if the ICD rate were to increase to 200 annually, biventricular pacing could add another $2.1 million to the hospital budget.

Recent non-randomized trials of similar populations suggest a first year mortality rate of 30%, a 52% mortality rate over 3 years, and a 64% mortality rate over a five-year period[41 42] Based on this information, we estimate that approximately 20% of the patients may survive

longer than 6 years, and these patients will probably have the device replaced on the 7th year post-implantation, resulting in an increase in future costs.

4. Discussion

Several randomized controlled trials have been performed to evaluate biventricular pacing but only a narrow patient population has been adequately examined. In particular the following entrance criteria have been generally adhered to:

1. Patients with ejection fraction < 35%, NYHA III/IV, QRS > 130 mseconds, and in normal sinus rhythm.
2. Pre-implant evaluation suggesting a significant reduction in quality of life but with projected life expectancy greater than 6-12 months.
3. Patients remaining symptomatic despite maximal pharmacologic (digoxin, diuretics, beta-blockers, spironolactone, ace inhibitors and/or angiotensin II receptor antagonists).

Each of these elements requires some additional discussion. First, recognizing the inexactitudes of the NYHA classification for judging patient incapacity, the University of Toronto has adopted a policy whereby all potential patients must undergo a 6MWT and attain less than 400 meters (P Dorion, presentation RVH, Dec 18 2003). The importance of assuring optimal medical therapy before consideration of CRT can't be overstated. In the Higgins' study[19] 50% of NYHA III/IV patients improved to NHYA I/II after device implantation but in the one month before the biventricular pacing was activated, simply by optimization of their pharmacologic treatment and possibly a placebo effect. No study has specifically considered the benefits of non-pharmacologic (smoking cessation, weight reduction, exercise training programs) interventions on patient outcomes. As patients qualifying for a biventricular pacemaker also qualify for an ICD (MADIT 2 criteria[43]), it appears illogical to implant a biventricular pacemaker alone as this would address only quality of life without addressing potential length of life.

There is also insufficient evidence to apply this therapy to patients in atrial fibrillation or to patients with only mild CHF symptoms (NYHA I/II). Mortality rates in patients

with CHF and NYHA class IV remain high despite the use of CRT (53% at 8 months)[7], which stresses the dilemma of selecting patients with an appropriate disease severity if one hopes to realize any quality of life benefits with this technology. To assure a potential for gain, the University of Toronto does not implant these devices into NYHA IV who can't be improved by standard medical therapy.

Despite the different study designs and comparators, there is no evidence of a short-term (6 month) survival benefit with CRT. Some studies have shown an approximately 50% reduction in subsequent heart failure hospitalizations in patients using biventricular pacing compared to no pacing after 6 months of treatment[14 15] However, the most contemporary and pertinent studies comparing CRT+ICD versus ICD alone showed no difference in hospitalizations[18 19 32].

The results of the published studies do suggest an improvement in quality of life, as measured by LHFQ, 6MWT, NYHA functional class, with biventricular pacing with and without ICD compared to no pacing or univentricular pacing after 3-6 months of treatment. The results of the studies also suggest improvements in the LHFQ and NYHA functional class with biventricular pacing with ICD compared to ordinary ICDs. For the 6MWT, it appears that while the difference between the two groups is statistically significant, it is only about 20 meters. This may be an example of where care must be taken not to make the measureable important but rather to measure the important. The 6MWT and LHFQ scales have shown a low responsiveness to changes in the patients' clinical status. Furthermore, their validity has been inconsistent, especially in patients with NYHA functional classes III and IV[44 45 46]It is therefore difficult to correlate the improvements observed in the 6MWT and with the LHFQ with improvements in the patients' daily life activities [44 45 46].

It should be recalled that the quality of life improvements observed in the RCTs are averaged over both responders and the approximately 30-40% of non-responders. This implies that certain patients experience a larger and clinically more important improvement in quality of life. This confirms anecdotal local clinical experiences (Dr. N. Racine – Institute

de Cardiologie de Montréal) and experience in the medical literature where cardiac transplantation has been delayed or even occasionally foregone. Unfortunately, there are no definitive studies to predict which patients are likely to respond[22 47 48]although research to identify echocardiographic predictors of a positive response is ongoing.

Fortunately, there are a number of other interventions for patients with congestive heart failure that improve mortality as well as quality of life and should be systematically applied before considering biventricular pacing. These interventions have a more solid evidence base, are less costly than biventricular pacing, and include pharmacologic and non-pharmacologic therapies[49], as outlined in an algorithm presented in Appendix 13. This algorithm positions the panoply of available CHF treatments and suggests that the majority of patients will attain clinical stability before requiring biventricular pacing. Both mortality and morbidity is reduced when care is supplied by specialized heart failure clinics without recourse to biventricular pacing and should be the cornerstone of care for MUHC CHF patients[50 51].

The additional first-year cost of implanting one biventricular pacemaker with ICD compared to standard ICDs was $10,442. Cost-effectiveness analysis for this technology is very problematic as there are no mortality advantages, and estimates of utilities to calculate quality-adjusted life years are unreliable[52]. If biventricular pacing with ICD did lead to reduced hospitalizations compared to ordinary ICDs, these savings would obviously offset part of the additional costs. However, the cost-savings obtained with fewer hospitalizations may not be fully realized by the MUHC, as the hospitalizations may occur in other institutions. Moreover, biventricular pacing with ICD did not show any reduction in hospitalizations compared to ICDs, at least during the 6 months of follow-up[18 19 32].Given the absence of mortality benefits and the additional expenses, it is not recommended that already pre-implanted ICDs be replaced by CRT-ICDs. This would amount to an additional $30,000 investment for uncertain QOL benefits.

The opportunity cost associated with the use of this technology must be considered. Given the fixed budget of the cardiology department with a fixed allocation for pacemakers,

this additional expense means that for every 2 combined CRT-ICD devices installed, there is a budget reduction corresponding to 1 fewer ICD, which have been shown to significantly improve survival in very similar patients (http://upload.mcgill.ca/tau/icd.pdf). If there were 6 combined CRT-ICD installations over the next 12 months, the additional $60,000 would likely have to be offset by the installation of 3 fewer ICD devices. If the hospital budget could be reallocated to cover this additional expense, it is unknown which resources would be eliminated. To give some sense of the size of the reduction of services involved, this sum theoretically could result in the closure of approximately 1 acute care medical bed for 6 months. If all projected 100 ICD implants for 2004 were upgraded to combined CRT-ICD units and financed through bed closure, 10 acute care medical beds would have to be closed for the entire year.

As there remain many questions about the final role of this technology including importantly the precise assessment of short and long-term benefits, durability and generalizability of the results, identification of promising patient subgroups, need to improve implantation techniques, and more elaborate cost-effectiveness studies, further research is indicated. However, in order for clinicians to participate in research on such an issue, they must be completely uncertain whether such treatment should be recommended or not, that is, in a state of "clinical equipoise". Both national and local clinical experts appear to have interpreted the literature of this new technology in a similar fashion to this report as researchers at the University of Ottawa, in a study funded by the Canadian Institute of Health Research, are proposing a long-term double-blinded clinical trial comparing biventricular pacing with ICD to ordinary ICDs alone[53]. Physicians at the MUHC who are participating in this trial appear to share this state of clinical equipoise.

Based on the lack of clinically meaningful differences identified to date, the current state of clinical equipoise and the consequent existence of ongoing research projects and the increased costs, TAU does not at this time recommend the routine approval of combined CRT/ICD technology at the MUHC. Despite this recommendation, it should not be concluded that there is no role for this technology at the MUHC as TAU firmly encourages

the participation of the MUHC in the Canadian Institute of Health Research funded Raft trial to further clarify the risks and benefits of this therapy.

TAU recognizes that unique cases may arise whereby a patient is ineligible for the current research project and that biventricular pacing is thought to be indicated. These highly selected patients would involve only patients regularly followed at the MUHC heart failure clinic who remain symptomatic despite optimal treatment. For these few exceptions, it is hoped that the present document will assist in identifying the patients most likely to obtain maximum benefit. The process of deciding which patients should receive this therapy is, of course, ultimately clinical. The Division of Cardiology has the necessary expertise in heart failure and arrhythmias and should continue their formal committee review of the indications and anticipated benefit for these few exceptional cases.

Recommendations:

Based on the lack of mortality benefits, the marginal impact on quality of life, the lack of long term results, the presence of ongoing research projects, and the considerable opportunity costs involved, the TAU does not recommend that the routine use of biventricular pacemakers with ICD be adopted at the MUHC.

TAU encourages the active participation of the MUHC in the CIHR funded trial which is further examining this technology. At present, TAU does not expect annually more than a maximum of 5 or 6 exceptional cases requiring biventricular pacing outside the context of the funded research trial.

Appendix 1

List of databases used in the literature search

- Pubmed
- Medline
- Cochrane database

Health Technology Assessment Agencies:

- CHSPR – Centre for Health Services and Policy Research (UBC) British Columbia
- HSURC – Health Services Utilization and Research Commission (Saskatchewan)
- ICES – Institute for Clinical Evaluative Sciences
- MCHP – Manitoba Centre for Health Policy
- INAHTA database – International Network of Agencies for Health Technology Assessment

Members of INAHTA (agencies included in the INAHTA database):

AÉTMIS - Agence d'évaluation des technologies et des modes d'intervention en santé
AHFMR - Alberta Heritage Foundation for Medical Research
ANAES - L'agence nationale d'accréditation et d'évaluation en santé
ASERNIP-S– Australian Safety & Efficacy Register of New Interventional Procedures - Surgery
CAHTA - Catalan Agency for Health Technology Assessment and Research
CCOHTA – Canadian Coordinating Office for Health Technology Assessment
CÉDIT – Comité d'évaluation et de diffusion des innovation technologiques
CMT – Center for Medical Technology Assessment (Sweden)
DACEHTA – Danish Centre for Evaluation and Health Technology Assessment
DIMDI – German Institute of Medical Documentation and Information
DSI – Danish Institute for Health Services Research
FinOHTA – Finnish Office for Health Care Technology Assessment
ITA – Institute of Technology Assessment ((Austria)
MSAC – Medical Services Advisory Committee (Australia)
NCCHTA - National Coordinating Centre for Health Technology Assessment
NHS QIS - NHS Quality Improvement Scotland
NHS – National Horizon Scanning Centre
N.I.C.E. – National Institute for Clinical Excellence
SBU – The Swedish Council on Technology Assessment in Health Care
SNHTA – Swiss Network for Health Technology Assessment
TA-SWISS – Center for Technology Assessment

Websites:

- FDA (www.fda.gov)
- The heart.org (www.theheart.org)
- Clinical trial results (www.clinicaltrialresults.com)

APPENDIX 2

Description of the studies used in the report

Higgins et al. published a randomized, double-blind trial comparing active biventricular pacing with ICD mechanism against inactive biventricular pacing with active ICD mechanism[19 31]. The study started with a crossover design of 3 months follow-up and was then modified to a parallel group design with 6 months follow-up[19]. Patients with an indication to an ICD, NYHA functional class II-IV, QRS $\geq$ 150, left ventricular ejection fraction (LVEF) $\leq$ 35%, and normal sinus node function were included, and patients with chronic, medically refractory atrial tachyarrhythmias were excluded from the trial[19 31]. From the 581 patients initially enrolled in this study, 91 (15.7%) did not proceed into the randomized phase of the study, 14 (2.4%) withdrew their consent, in 66 (11.4%) patients, implantation of the device was unsuccessful, and 10 (2%) patients died between the implantation of the device and randomization, however it was not specified if these deaths were caused by the device or its implantation procedure[19]. This study has not been published in a peer-reviewed journal.

The Miracle trial was a randomized, double-blind trial comparing biventricular pacing to no pacing in patients with NYHA functional class III or IV, LVEF $\leq$ 35%, left ventricular end-diastolic dimension (LVEDD) $\geq$ 55mm, QRS interval $\geq$ 130ms, and a six-minute walking distance $\leq$ 450m[14]. Patients were excluded if they had a pacemaker or a cardioverter-defibrillator[14]. After randomization, the patients were followed for six months, during which, changes in heart failure medication or crossover from the inactive to the active group were not allowed[14]. Five-hundred seventy-one patients were enrolled in the study, from which 118 (20.7%) did not continue into the randomized phase of the study due to: unsuccessful implantation in 43 (7.5%) patients, lack of consent to follow the long-term phase of the study in 71 patients (12.4%), and presence of exclusion criteria in 4 (0.7%) patients[14]. From the 225 patients randomized to the inactive device group, 24 (11%) did not complete the 6-month follow-up period due to death (16), heart transplantation (2), complications with the device (1), and for missing the visit (5), whereas in the active device group, from the 228 patients

randomized, 13 (6%) did not complete the 6-month follow-up period, due to death (12) and complications related to the device (1) [14].

The Miracle ICD trial was a randomized, double-blind, parallel controlled trial comparing the use of biventricular pacing with ICD, and ICD alone[18]. Patients with NYHA functional class III or IV, LVEF $\leq$ 35%, QRS duration $\geq$ 130ms, LVEDD $\geq$ 55mm, and that had cardiac arrest due to ventricular fibrillation or ventricular tachyarrhythmia, spontaneously sustained ventricular tachyarrhythmia, inducible ventricular fibrillation, or sustained ventricular tachyarrhythmia were included in the trial[18]. One hundred and eighty-seven patients were randomized to receive biventricular pacing plus ICD plus optimal medical treatment, and 182 patients were randomized to receive ICD plus optimal medical treatment for 6 months[18]. Fourteen percent of the 429 patients initially enrolled in the study did not undergo randomization due to: unsuccessful implantation of the device, 52 (12.2%) patients, presence of exclusion criteria, 6 (1.4%) patients, and death, 2 (0.4%). In the biventricular pacing plus ICD group, 22 (12%) patients did not complete the 6-month follow-up visit due to death (14), cardiac transplantation (2), and for having missed the visit (6), and 10 patients moved to the ICD alone treatment arm[18]. In the ICD alone group, 20 patients (11%) did not complete the 6-month follow-up visit due to death (15), or having missed the 6-month follow-up visit (5), and 14 patients moved to the biventricular pacing plus ICD treatment arm[18].

The Mustic trial was a randomized, single-blind, crossover trial in patients with NYHA class III, LVEF $\leq$ 35%, LVEDD $\geq$ 60mm, and QRS interval $\geq$ 150ms. Patients were excluded if they had an indication for a cardioverter-defibrillator[15]. The patients were kept on a 1-month observation period to verify the stability of heart failure, after which they were randomized to either active or inactive pacing for the first crossover phase[18]. Each crossover phase lasted for 3 months. From the 67 patients initially enrolled in the trial, 3 did not undergo implantation, two because of heart failure, and one because of a preexisting indication for pacing, six additional patients were not randomized due to implantation failure (5), and sudden death (1) [18]. Five patients did not complete the first crossover phase due to

withdrawal of consent (1), uncorrectable loss of left ventricular pacing efficacy (2), severe decompensation during inactive pacing (1), and death during active pacing (1) [18].

The Companion trial was a randomized, open-label comparison between optimal pharmacological therapy, optimal pharmacological therapy plus biventricular pacing, and optimal pharmacological therapy plus biventricular pacing plus ICD[13]. Patients had to present with heart failure and NYHA functional class III or IV, a QRS interval greater than 120 ms, a PR interval greater than 150 msec, and a LVEF $\leq$ 35%. Approximately 1630 patients were enrolled into the study, and were randomized with a 1:2:2 ratio to optimal pharmacological therapy, biventricular pacing, and biventricular pacing plus ICD respectively[13]. Information on the number of patients that dropped-out of the study or were lost to follow-up was not available. The investigators intended to enroll 2200 patients and follow them for 2 years[13]. The study was terminated prematurely in November 2002 by the study Data and Safety Monitoring Board, as the primary endpoint, consisting of a reduction in the composite of all-cause mortality and hospitalization was reached[13]. As the results of the Companion trial have not been published in a peer-reviewed journal yet, and the only information available is from press releases from conferences, its results should be interpreted cautiously.

The Path-CHF was a randomized, single-blinded study evaluated the effects of biventricular and univentricular pacing in patients with heart failure and NYHA class III or IV despite optimal therapy, QRS interval $\geq$ 120 ms, and PR interval $\geq$ 150 ms[29]. Patients with an indication for ICD or a conventional pacemaker were excluded from the trial[29]. The patients were randomized to receive treatment with either univentricular or biventricular pacing for 4 weeks, followed by a 4-week period with no treatment and another 4-week period with the opposite treatment[29]. The patients then continued to be treated for an additional 10 months with the treatment that was more effective according to the physician's judgement[29]. Due to the short controlled period of 4 weeks that could be used for a comparison between treatments, and the small sample size of 42 patients, this study was not included in our analysis, except for safety.

A meta-analysis including the Miracle, Insync ICD, Contak CD, and Mustic trials using biventricular pacing with or without ICD mechanism was performed[20]. As these two devices may have different efficacy, we have decided not to include the results of the meta-analysis in this report and to evaluate the outcomes of biventricular pacing and biventricular pacing with ICD mechanism separately.

APPENDIX 3
Studies Characteristics

Biventricular pacing

	Mustic[15]	**Mustic (Atrial fibrillation)**[17]	**Miracle** [14]
Inclusion Criteria	Idiopathic or ischemic LVSD LVEF < = 35% LVEDD > 60mm Sinus rhythm QRS > 150 ms No indication for pacemakers NYHA III for at least 1 month Optimal pharmacologicaltreatment	Persistent atrial fibrillation (>3months) requiring ventricular pacing LVEF < = 35% LVEDD > 60mm RV paced QRS >200ms NYHA III for at least 1 month Optimal pharmacological treatment 6MWT < 450m	NYHA III-IV Chronic heart failure due to ischemic or not cardiomyopathy LVEF < = 35% LVEDD > 55mm Sinus rhythm QRS > 130 msec 6MWT < 450 m Optimal pharmacological treatment stable for 1 month
Exclusion criteria	ICD indication Hypertrophic or restrictive cardiomyopathy Suspected acute myocarditis Correctable valvulopathy Acute coronary syndrome (< 3months) Coronary revascularization < 3m or scheduled Treatment resistant hypertension Severe obstructive lung disease Inability to walk Life expectancy < 1 year	ICD indication Hypertrophic or restrictive cardiomyopathy Suspected acute myocarditis Correctable valvulopathy Acute coronary syndrome (< 3m) Coronary revascularization < 3months or scheduled Treatment resistant hypertension Severe obstructive lung disease Inability to walk Life expectancy < 1 year	Pacemaker or ICD Indication or contraindication for cardiac pacing Cardiac or cerebral ischemic event within 3m Atrial arrhythmia within 1 month SBP < 80 or > 170 HR > 140 beats/min Serum creat >3mg/dl Serum hepatic fuction 3x ULN
Date published	March 2001	November 2002	June 2002
Comparator group	No pacing	Right-ventricular pacing	No pacing

LVSD=left ventricular systolic dysfunction / LVEDD=left ventricular end-diastolic diameter / LVEF=left ventricular ejection fraction / AF=atrial fibrillation
VT=ventricular tachyarrhythmias / 6MWT= 6-minute walk test / RV=right ventricle

Biventricular pacing with ICD mechanism

	Higgins et al. [19]	Miracle ICD[18]	Companion[13]
Inclusion Criteria	ICD indication LVEF < = 35% Sinus rhythm QRS >= 120 msec Optimal treatment Symptomatic heart failure	Cardiac arrest due to VF or VT, or spontaneously sustained VT or inducible VF or sustained VT NYHA III-IV QRS >=130 LVEDD >=55mm Stable pharmacological treatment > 1 month	NYHA III-IV 6m and 1 of the following within 12m: -Hospitalization for heart failure - IV inotropes or vasoactive drugs administered continuously for 4hours -ER visit with IV HF medications QRS >= 120ms PR > 150 ms LVEF <= 35% LVEDD >= 60 mm Life expectancy> 6m Optimal pharmacological treatment
Exclusion Criteria	Pacemaker dependance Chronic medically refractory tachyarrhythmias Concomitant cardiac surgery Unable to undergo device implant (anesthesia) Unable to walk Life expectancy < 6m Hypertrophic obstructive cardiomyopathy Require in-hospital IV inotropes Tricuspid prosthesis	6MWT > 450m Unstable angina, AMI, revascularization, CVA/TIA 3m Bradycardia requiring pacemaker Severe valvular disease Life expectancy < 6m Severe pulmonary disease SBP < 80 or > 170 Heart transplant Resting HR > 140 bpm Serum creatinine >3mg/dl Serum hepatic function 3x ULN	ICD indications Antibradycardia pacing indications Heart transplantion expected within 6 m Chronic, medically refractory atrial tachyarrhythmias MI within 6 months of randomization History of noncompliance SBP > 160 mmHg or < 85 mm Hg or DBP > 90 mm Hg Surgically uncorrected primary valvular heart disease CAD with revascularization within 60 days Progressive or unstable angina See reference for further exclusion criteria
Date published	October 2003	May 2003	Estimated: December 2003
Comparator group	ICDs	ICDs	No pacing

AF=atrial fibrillation / AMI=acute myocardial infarction / CAD=coronary artery disease / CVA= cerebrovascular accident / ER=emergency room visit / HR=heart rate LVEDD=left ventricular end-diastolic diameter / LVEF=left ventricular ejection fraction / LVSD=left ventricular systolic dysfunction / MI=myocardial infarction 6MWT= 6-minute walk test / TIA=transient ischemic attack / ULN=upper limit of normality / VT=ventricular tachyarrhythmias

Appendix 4

Validity and reliability of instruments used to measure quality of life

The Minnesota living with heart failure questionnaire (LHFQ) was the instrument used to measure quality of life in the published studies. This scale assesses the patients' perception of how their emotional and physical state is impaired by heart failure[33]. The questionnaire has 21 questions that evaluate the physical and emotional limitation, and the total score varies from 0 to 105, with higher scores representing a more severe impairment[33]. The validity and the reliability of this scale have been documented[44]. Riegel et al. studied the sensitivity of the LHFQ to clinical differences and its responsiveness to change in patients with heart failure[44]. Data from nine trials in heart failure in eight sites in the United States was pooled, totaling 1136 patients analysed[44]. The two measures of disease severity used were NYHA functional class and left ventricular ejection fraction[44]. The LHFQ was able to detect differences both in the total and subscale scores between patients in NYHA classes I, II, and III ($p<0.001$), however, with the exception of the physical subscale, it was not possible to differentiate between patients in NYHA classes III and IV[44]. Bennet et al. reached similar conclusions after evaluating a sample of 211 patients with heart failure with the LHFQ[34]. No statistically significant differences were seen in total or subscale scores of patients with different levels of left ventricular ejection fraction, i.e., <=40%, 41-49%, and >=50%[44].

The 6-minute walk test (6MWT) is used to evaluate the functional capacity in patients with congestive heart failure[45]. The reliability and the validity of the 6-minute walk test (6MWT) was evaluated in a study that included 768 patients with heart failure and LVEF lower than 40%, and that were able to walk less than 500 m during the test[46]. Although the authors considered the reliability of the test very good to excellent, i.e., an intraclass correlation coefficient of 0.85, the construct validity was considered only moderately inversely correlated with the NYHA functional class, i.e., $r = -0.43$ ($p=0.001$), and the responsiveness to change was considered small[46]. In a study including 113 patients with LVEF lower or equal to 35%, and with NYHA classes I to III, the 1-year mortality was higher in patients that were able to walk only a shorter distance during the 6MWT, i.e., 57% in patients who walked less than 300 m, and 24% and 8% in patients who walked

between 300-450 m and more than 450 m respectively[45]. Studies using the 6MWT in patients with congestive heart failure showed inconsistent results regarding its prognostic value[54].

The NYHA assesses the effect of cardiac disease on patients with heart failure[34]. According to Bennet et al., findings from studies in the literature showed a moderate correlation between the NYHA functional classes and the VO2 max exercise capacity, however, patients with NYHA classes III and IV still had variable oxygen consumption capacity at peak exercise[34]. Moreover, in a reliability study using a sample of 75 patients, it was shown that the evaluation of the NYHA functional class by two physicians (a cardiologist and the patient's physician) agreed only 56% of the time[34].

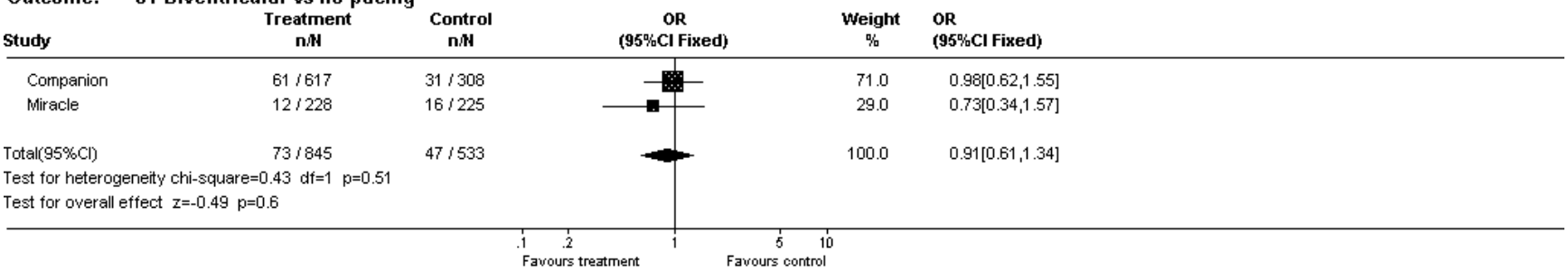
Appendix 5

Randomized, controlled trials
Biventricular pacemakers vs. no pacing
Patients were receiving optimal pharmacological therapy*

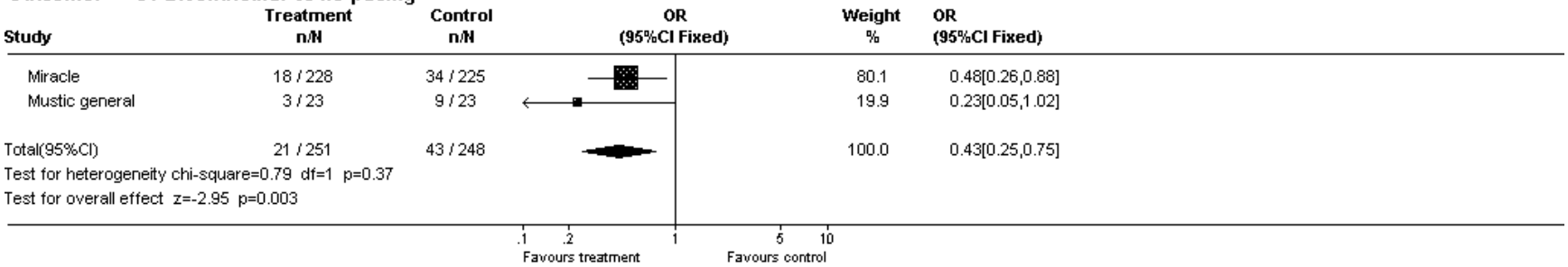
Study (N) Design/f-up	All-cause mortality N (%)	Heart failure hospitalizations # hospitalizations (%)	Heart failure hospitalization # patients (%)	NYHA Functional class change	Change in Quality of Life	Change in 6-min walk
Miracle[14] (N=453) Biventricular: 228 pts Control: 225 pts. Double-blind / 6m	**B:** 12 (5.3%) **C**: 16 (7.1%)	**B**: 18 (7.9%) **C**: 34 (15.1%)	**B**:12% **C**: 19.6%	**Improv >1 class:** **B**: 143 (68%) **C:** 74 (38%)	**B**: -18 (-22 , -12) **C**: -9 (-12 , -5) p=0.001	**B:** +39 m (26 , 54) / **C**: +10 m (0 , 25) p=0.005
Mustic[15] (N=58) Crossover, Single-blind / 3m	**B**: 2 (3.4%) **C**: 0	**B**: 3 (12%) **C**: 9 (19.6%)	-	-	**B**: -13.2 43.2+-23 (baseline) p<.001	**B**: +74 m 325 +-134 m (baseline) p<.001
Mustic[16] (N=48) Synus rhythm Crossover, Single-blind/12m	-	**B:** 0.02 hospitalizations / month **C**: 0.14 hospitalizations / month	-	**B:** 2.1+-0.5 Baseline: 2.8+-0.4 p=.0001	**B**: -16 (6m) **B**: -17 (12m) 47+-23 (baseline) p=.0001	**B**:+ 42 (6 months) **B**: +70 m (12 months) 348+-98 m (baseline) p=.0001
Companion[35,37] (N=1520) Open label/12m Biventricular: 617 pts. C: 308 pts.	**12 months** **B:** 93 (15%) **C**: 56 (19%) P=0.06 **6 months (information drawn from the survival curve)** **B:** 61 (10%) **C**: 31 (10%)	**12 months** **(# pts hospitalized)** **B:** 247 (40%) **C**:153 (49%) (information drawn from the composite endpoint and all-cause mortality results)	**12 months** **B:** 340 (55%) **C:** 209 (68%) p=0.008	-	-	-

B=Biventricular / C=Control
*Optimal pharmacological therapy consisted a diuretic, an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor blocker, a digitalis and a beta-blocker
AF=atrial fibrillation / DB=double-blinded / HR: hazard ratio / LVEDD=left ventricular end-diastolic dimension / OL=open label / SB=single-blinded
(-) information not available

Comparison: 01 All-cause mortality - 6 months
Outcome: 01 Biventricular vs no pacing



Comparison: 02 Heart failure hospitalizations - 6 months
Outcome: 01 Biventricular vs no pacing



APPENDIX 6

Randomized, controlled studies comparing Biventricular pacemakers vs. univentricular pacemakers
Patients were receiving optimal pharmacological therapy*

Patients with atrial fibrillation

Study (N) **Design/f-up** **Comparator**	**All-cause mortality**	**Heart failure hospitalizations** **# hospitalizations** **(%)**	**NYHA Functional class change**	**Change in Quality of Life**	**Change in 6-min walk**
Mustic[16] (N=41) Crossover, single-blind /12m vs right univentricular adaptive ventricular inhibited pacing	-	**B:** 0.04 hospitalizations / month **C:** 0.14 hospitalizations / month	**B**: 2.2+-0.5 Baseline: 3+-0 p=.0001	**B**: -14 45+-23 (baseline) p=.002	**B**: +50 m 315+-80 (baseline) p=.004
Mustic[17] (N=43) Atrial fibrillation Crossover, single-blind / 6m Vs. Right ventricular pacing	**B**: 1 (2.3%) **C**:0	**# pts hospitalized** **B**: 3 (7%) **C**: 10 (23%) OR:0.25 (0.06 , 0.97)	-	**B**: -12.4 **C**: -8.1 p=0.11 Baseline: 46+-22	**B:** +50 m **C**: +18 m p=0.05 Baseline: 324 +-76 m

*Optimal pharmacological therapy consisted a diuretic, an angiotensin-converting-enzyme inhibitor or an angiotensin-receptor blocker, a digitalis and a beta-blocker
SB=single-blinded / DB=double-blinded / OL=open label / AF=atrial fibrillation / LVEDD=left ventricular end-diastolic dimension
(-) information not available

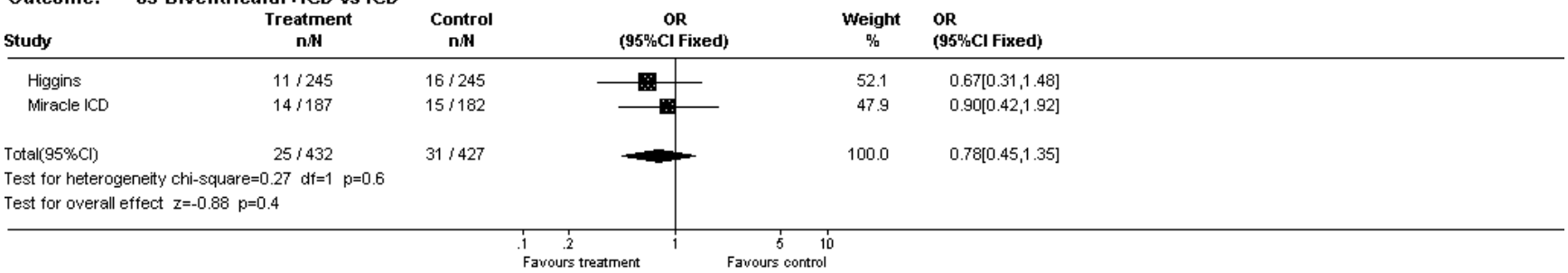
APPENDIX 7
Randomized-controlled studies comparing Biventricular pacemakers with ICD vs. no pacing
Patients were receiving optimal pharmacological therapy

Study (N) **Design/f-up**	All-cause mortality **N (%)**	**Heart failure hospitalizations** **# hospitalizations (%)**	**Heart failure hospitalization and mortality**	**Functional class change** **NYHA III/IV (n=93)**	**Change in Quality of Life** **NYHA III/IV (n=93)**	**Change in 6-min walk** **NYHA III/IV (n=93)**
Companion[35,37] N=595) Open label/12m B-ICD:595 C: 308	**12 months** **B-ICD**: 71 (12%) **C** : 59 (19%) P=0.003 HR:0.64 (95% CI:0.48 , 0.86) **6 months (information drawn from survival curve** **B-ICD**: 42 (7%) **C** : 31 (10%)	**# pts (%)** **B-ICD**: 94 (16%) **C**: 85 (28%)	**B-ICD**: 333 (56%) **C**: 209 (68%) p=0.007	-	-	-

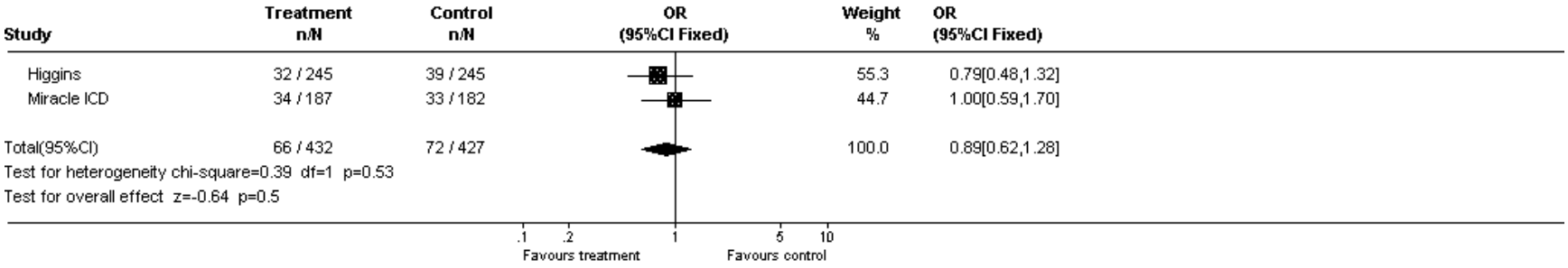
APPENDIX 8
Randomized, controlled studies comparing Biventricular pacemakers with ICD vs. ICDs
Patients were receiving optimal medical therapy

Study (N) Design/f-up Comparator	All-cause mortality (f-up) n (%)	All-cause / Heart failure hospitalizations n (%)	Mean NYHA Functional class change	Mean Change in Quality of Life	Mean Change in 6-min walk
Miracle ICD[18] (N=369) Double-blind / 6m B-ICD:187 pts C: 182 pts	**B-ICD** : 14 (7.6%) 3 (21%) - sudden death **C** : 15 (7.8%) 3 (20%) – sudden death p=0.96	***All-cause hospitalizations*** **B-ICD**: 85 pts (45.5%) **C**: 78 pts (42.9%) p=0.69 *Heart failure hospitalizations(information drawn from the composite endpoint result)* **B-ICD**:34 pts (18%) **C**: 33 pts (18%)	**Improvement >= 1 class** **B-ICD**:117 (63%) **C**:91 (50%) **B-ICD :** -1 (3.1 at baseline) **C**: 0 (3.1 at baseline) (p=0.007)	**B-ICD**: -17.5 (56.8 at baseline) **C:** -11 (55.2 at baseline) (p=0.02)	**B-ICD:** +55 m (243 m at baseline) **C:** +53 m (243 m at baseline) (p=0.36)
Higgins[19] (N=490 / 227) NYHA I-IV: (B-ICD:245 / C:245) NYHA III-IV: (B-ICD:117 / C :110) Double-blind / 6m	**Classes I-IV** **B-ICD:** 11 (4.5%) **C:** 16 (6.5%) **Classes III-IV** Not available	**Classes I-IV** **B-ICD:** 32 (13%) **C:** 39 (15.9%) **Classes III-IV** Not available	**Classes I-IV** **B-ICD**: 88 (36%) **C:** 78 (32%) **Classes III-IV** **B-ICD**: 87 (74%) **C:** 59 (54%)	**Classes I-IV** **B-ICD:** -7 (44 at baseline) **C:** +5 (40 at baseline) **Classes III-IV** **B-ICD**: -16 (56 at baseline) **C**: -5 (49 at baseline)	**Classes I-IV** **B-ICD:** +35 (316 at baseline **C:** +15 (320 at baseline) **Classes III-IV** **B-ICD**: +60 m (268 m at baseline) **C**: +20 m (269 m at baseline)

Comparison: 01 All-cause mortality - 6 months
Outcome: 03 Biventricular+ICD vs ICD



Comparison: 02 Heart failure hospitalizations - 6 months
Outcome: 04 Biventricular+ICD vs ICD



APPENDIX 9
Non-randomized studies
Patients were receiving optimal medical therapy

Biventricular Pacemakers - no comparator

Study (N) Design/f-up	All-cause mortality (f-up)	Hospitalizations	Change in NYHA	Change in Quality of life	Change in 6-min walk
Leclercq[2] (125) Consecutive patients / 22m	20% (12m) 26% (22m)	-	2.3+-0.8 / 3.3+-0.5(baseline)	-	-
Molhoek[21] (40) Consec.utive patients	12.5% (11.2m)	**For heart failure** 0.5+-1.5 days / 3.9+-5.3 (before) 0.1+-0.3 hosp/yr / 0.8+-1.1 (before) p<.05	2.1 +- 0.8 / 3.3 +-0.5(baseline) p<0.05	-14 Baseline: 42+-14 p<0.05	+138 m (262+-92 at baseline) p<0.05
Reuter[22] (47) Consecutive / 8m	15% (8m)	-	-	-	-
Leon[23] (20) Consecutive patients /12m	-	**All-cause hospitalization** 0.4+-0.6 / 1.9+-0.8 (before) p<.001	2.4 +- 0.6 / 3.4 +-0.5(baseline)	-26 Baseline: 78+-24 (p<.01)	-
Gras[24] (102) Consecutive patients / 12m	-	-	2.2+-0.68 / 3.3+-0.4	-22 Baseline : 53+-20 P<.001	Active: +75 m (290+-108 at baseline) p<.001

(-) information not available

Biventricular vs. left ventricular (LV) pacing

Study (N) Design/f-up Comparator	Month / Year of publication in peer-reviewed journal	Change in NYHA	Change in Quality of life	Change in 6-min walk
Touiza[25] (33) Consecutive patients /6m x LV pacing	12/2001	B: -1.3 Left ventricular: -1.1 p=0.63	-	B: +58+-103 (423+-72 at baseline) Left ventricular: +15+-81 (409+-88 at baseline) p=0.3

(-) information not available

Biventricular-ICD / no comparator

Study (N) Design/f-up Comparator	All-cause mortality (f-up) Active/control	HF hospital. Active/control	QOL	6-min walk
Kuehlkamp[26] (84) Consecutive patients / 3m	6% - 6m	-	Active : -16.5 (45.4 +-19.6 at baseline) (Classes III/IV 3m)	Active :+ 89 m (357 +-122 / 268 +-112 at baseline) (Classes III/IV 3m)
Gasparini[27] (142) Consecutive patients / 24m	5% (6m) 13% (12m) 31% (24m)	-	-	-

(-) information not available

Biventricular-ICD vs Biventricular pacemakers

Study (N) Design/f-up Comparator	Non-HF mortality (f-up) Active/control	All-cause mortality (f-up) Active/control	QOL	6-min walk
Pappone[28] (135) Consecutive patients / 12m	HR: 0.08 (0.05 , 0.42) for sudden death - BVP+ICD	HR:0.76 (0.56 , 0.96) for BVP+ICD At 1 yr 4% - BVP+ICD 13% - BVP	-	-

(-) information not available

Appendix 10

Rates of complications during and after the implantation procedures with biventricular pacing with or without ICD

Adverse event	InSync ICD[32] % pts N=371 / 421 for implantation	Contak CD [31]6m % pts N=517	Ricci [38]10m N=190	Miracle ICD[18] During impl % pts N=429	Miracle[14] % pts N=571	Kuehlkamp[26] 3m % pts N=84	Mustic[15](3m) % pts N=58	Insync[24](12m) % pts N=103	Path-CHF[39] (12m) % pts N=41	Leclercq[2] (22m) % pts N=125	Taieb[40] (6m) % pts N=50
DURING THE PROCEDURE											
Device-related events/patient * (including both observations and complications)	-	36%	-	-	-	-	-	-	-	-	-
Unsuccessful implantation	10.9% (if classes II – IV are included)	11.4%	11%	12.2%	7.5%	3.6%	9%	12%	-	10%	-
Reinterventions necessary	-	-	-	-	-	-	-	-	-	21%	-
LV lead dislodgement	5.7%	-	-	-	-	1.2%	-	-	-	-	-
Asystole	-	-	1.4%	-	0.2%	-	-	-	-	-	-
A. fibr.	1.0%	-	-	-	-	-	-	-	9.8%	-	-
Atrial flutter	0.5%	-	-	-	-	-	-	-	-	-	-
AV Block	-	1.4%	-	-	-	-	-	-	-	-	-
Cardiac perforation	1.2%	-	-	0.9%	-	-	-	-	-	-	-
Cardiac tamponade	-	-	0.9%	-	-	-	-	-	-	-	-
Coronary sinus dissection	4%	1%	3.8%	3.5%	4%	-	-	-	-	2.4%	0
Coronary sinus perforation	3.3%	-	-	-	2%	-	-	0.9 %	-	-	0
Coronary venous perforation	-	1%	-	-	-	-	-	-	-	-	-
Diaphragm stimulation	0.5%	-	-	-	-	-	-	-	-	-	-
Exit block	-	-	-	-	-	-	-	-	7.3% due to incr. stimul thresholds	-	-
Elevated pacing thresholds	-	-	-	1.6%	-	-	-	-	-	12%	-
Heart block	2.9%	-	-	0.7%	0.4%	-	-	-	-	-	-
Hematoma	-	2.1%	-	-	-	3.6%	-	-	-	-	-

Hematothorax	-	-	-	-	-	1.2%	-	-	-	-	-
HF decomp.	0.7%	-	-	1.4%	-	-	-	-	-	-	-
Hypotension	0.7%	1.4%	-	-	0.2%	-	-	-	-	-	-
Infection, post-op.wound	-	1.4%	-	-	1.2%	1.2%	-	-	-	2.4%	-
P-wave lead oversensing	-	-	1.6%	-	-	-	-	-	-	-	-
Patient decompensation	0.7%	-	-	-	-	-	-	-	-	-	-
Pericardial effusion	-	-	0.9%	0.5%	-	-	-	-	-	-	-
Pericarditis	-	-	-	0.2%	-	-	-	-	-	0.8%	-
Pneumothorax	-	1.4%	-	0.7%	-	3.6%	-	-	-	-	-
Post surgical wound disconfort	-	1.9%	-	-	-	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	1.2%	-	-	-	-	-
Renal failure	-	1%	-	-	-	-	-	-	-	-	-
VT	1.2%	-	1.4%	1.2%	-	-	-	-	-	-	-
AFTER THE PROCEDURE											
AV Block	-	0.5%	-	-	-	-	-	-	-	-	10%
Arrhythmia –SVT	-	9.4%	-	-	-	-	-	-	-	-	-
Arrhythmia – VT	-	3.9%	-	-	-	-	-	-	-	-	-
Arrhythmia – Brady	-	3.1%	-	-	-	-	-	-	-	-	-
Atrial arrhythmias	1.7%	-	-	-	-	-	-	-	-	-	-
Cardiac arrest	-	0.4%	-	-	-	-	-	-	-	-	-
Chest pain	-	5.8%	-	-	-	-	-	-	-	-	-
Coagulopathy	-	0.5%	-	-	-	-	-	-	-	-	-
CHF	1.2%	27%	-	-	-	-	-	-	-	-	-
Coronary lead fracture	-	-	-	-	-	-	-	-	-	-	4%
Device migration	-	-	-	-	-	1.2%	-	-	-	-	-
Distal thromboemboli	-	0.58%	-	-	-	-	-	-	-	-	-
Dizziness	9%	3.3%	-	-	-	-	-	-	-	-	-
Dyspnea	1.2%	3.1%	-	-	-	-	-	-	-	-	-
Fatigue	7%	1.9%	-	-	-	-	-	-	-	-	-
Hypertension	-	0.2%	-	-	-	-	-	-	-	-	-
Hypotension	7%	21%	-	-*	-	-	-	-	-	-	-
ICD implantation	-	-	0.5%	-	-	-	-	-	-	-	-
Infection of ICD/lead	-	-	1%	-	-	2.4%	-	0.9%	-	-	2%
Lead dislodgement (right atrium)	-	-	1%	-	-	1.2%	-	-	-	-	-

Lead dislodgement (left ventricle)	-	-	7.4%	-	-	7.1%	-	16%	-	-	16%
Loss of BV pacing capture	-	-	-	-	-	-	-	2.6%	-	-	-
Myocardial infarction	-	0.4%	-	-	-	-	-	-	-	-	-
Painful pulse generator pocket (requiring withdraw)	-	-	-	-	-	-	-	0.9%	-	-	-
Pacemaker syndrome	-	0.2%	-	-	-	-	-	-	-	-	-
Palpitations	3.8%	0.4%	-	-	-	-	-	-	-	-	-
Pericardial effusion	0.5%	0.6%	-	-	-	-	-	-	-	-	-
Phrenic stimulation	-	-	2.1%	-	-	-	-	-	-	-	-
Pleureal effusion	1.6%	-	-	-	-	-	-	-	-	-	-
Pulmonary edema	-	1.2%	-	-	-	-	-	-	-	-	-
Shock	-	0.8%	-	-	-	-	-	-	-	-	-
Stimulation of the diaphragm	-	-	-	-	-	1.2%	-	0.9%	-	-	-
Stroke syndrome or CVA	2.2%	0.8%	-	-	-	-	-	-	-	-	-
Syncope	2.2%	1.7%	-	-	-	-	-	-	-	-	-
Thrombosis	-	0.5%	-	-	-	-	-	-	-	-	-
Vascular related	-	1%	-	-	-	-	-	-	-	-	-

*Device related events included: migration of device, pacemaker mediated tachycardia, telemetry difficulty, loss of capture, inappropriate shock due to oversensing, insulation breach, multiple counting, phrenic nerve/diaphragm stimulation, undersensing, elevated DFTs, inappropriate shock above rate cutoff or oversensing, non-conversion of VF, phantom shock.

Device-related events included both observations and complications, reported separately by the authors

(-) information not available

Appendix 11
Individual costs used in the cost analyses with biventricular pacemakers with or without ICD mechanism

Costs associated with the successful implantation of the device

Device cost =,$32,805 (adjusting for lead dislodgement events and unsuccessful implantations)

$31,100 (CRT-ICD)

and, allowing for a 5% wastage of the device and lead:

+ $150 (=$3,000*5% lead dislodgement cost + $1,555 ($31,100*5% - assuming that half of the 10% unsuccessful implantations would not re-use the device**)

** According to Gras[24] et al. and Leclercq et al[2]., part of the devices was replaced, and part could be re-used after adverse events such as infected device.

Implantation procedure cost = $ 386.4

Salary per hour - $28 * 3 hours * 4 professionals, i.e. 2 nurses and 2 technicians (including unsuccessful implantations)

Post-implantation hospital stay = $ 1,000

(1 day in ICU, reference: Dept. of Finance)

Pneumothorax: $44.60

$3,430 x 0.013 (complication rate from Appendix 10)

(Chest drainage in recovery room for 24 hours $28/2x24 plus 7 days in the surgical ward – 7x $442 - based on the TAU ICD report – http://upload.mcgill.ca/tau/icd.pdf)

Perforation of the coronary sinus: $441

$ 7,000 x 0.063 (rate of coronary sinus or coronary venous perforation, and coronary sinus dissection from Appendix 10)

($7,000 assumed to be equivalent to CABG of mild to moderate severity - based on the TAU ICD report – http://upload.mcgill.ca/tau/icd.pdf)

Total cost associated with the CRT implantation procedure: $ 34,677

Treatment of complications after the CRT implantation procedure

Infection of the ICD/lead: $237.1

$386.4 (implantation procedure) + $ 1,000 (post-implantation hospitalization) = $1,386.4 * 0.014 (rate of occurrence – appendix 10) + $217.7 ($30,100*0.007 – assuming that in half of the patients with this complication, a new device will have to be used, the other half is assumed to have the device re-used).

Repositioning of the right or left ventricular lead: $381

$386.4 (implantation procedure) + $ 1,000 (post-implantation hospitalization)= $1,386.4 * 0.132 (rate of occurrence of lead dislodgement plus phrenic stimulation – appendix 10) + $198 ($3,000*0.066 – assuming that in half of the patients with this complication, a new lead will have to be used, the other half is assumed to have the device re-used).

Reprogramming of the generator: $13.86

$386.4 (implantation procedure) + $ 1,000 (post-implantation hospitalization)= $1,386.4 * 0.01 (rate of occurrence of stimulation of the diaphragm – Appendix 10).

Device migration: $355.66

$386.4 (implantation procedure) + $ 1,000 (post-implantation hospitalization)= $1,386.4 * 0.021 (rate of occurrence of device migration and painful pulse generator – Appendix 10) + $326.55 ($30,100*0.0105 – assuming that in half of the patients with this complication, a new device will have to be used, the other half is assumed to have the device re-used).

Total cost for complications after the CRT implantation procedure: $ 987.62

As no specific data in the literature was available regarding the actual rate of replacement of device or leads for complications such as device migration, lead dislodgement, and device/lead infection, we assumed that in half of the patients the same lead/device would be utilized, and the other half would require a new device or lead.

Appendix 12

American College of Cardiology Foundation and the American Heart Association recommendation guidelines[10]

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

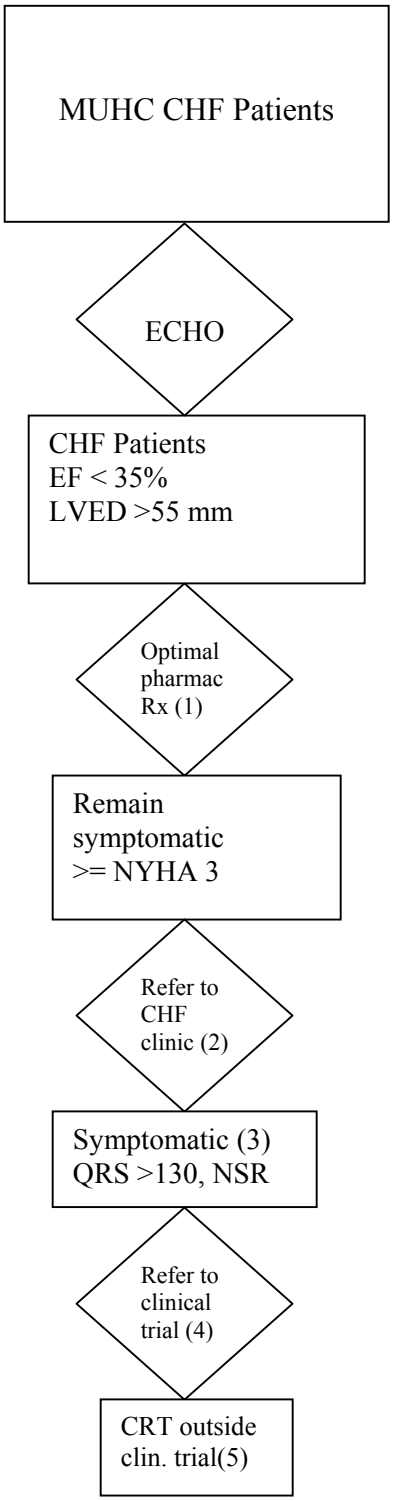
Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Table ACC/AHA Pacing Recommendations for Dilated Cardiomyopathy

Class I Indications for sinus node dysfunction or AV block as described previously. *(Level of Evidence: C)* Class IIa Biventricular pacing in medically refractory, symptomatic NYHA class III or IV patients with idiopathic dilated or ischemic cardiomyopathy, prolonged QRS interval (greater than or equal to 130 milliseconds), LV end-diastolic diameter greater than or equal to 55 mm, and ejection fraction less than or equal to 35%. *(Level of Evidence: A)* Class III 1. Asymptomatic dilated cardiomyopathy. 2. Symptomatic dilated cardiomyopathy when patients are rendered asymptomatic by drug therapy. 3. Symptomatic ischemic cardiomyopathy when the ischemia is amenable to intervention.

Appendix 13

Algorithm showing the sequential selection of potential CHF candidates for biventricular pacing



Algorithm showing the sequential selection of potential CHF candidates for biventricular pacing and the consequently limited role for biventricular pacing at the MUHC

(1) Optimal pharmacologic therapy involves digoxin, diuretics, ACE inhibitors, bets blockers, spironolactone and AT blockers (especially if intolerant to ACE inhibitors)

(2) CHF clinic facilitates pharmacologic (2^{nd} diuretic, periodic intravenous diuretics and inotropic support) and non pharmacologic treatment of CHF (smoking cessation, dietary counseling with attaining ideal weight, exercise program)

(3) The severity of symptoms must be objectively determined with 6MWT

(4) University of Ottawa CIHR sponsored trial

(5) It is assumed that a small number of patients may not participate in the clinical trial for a variety of reasons but may still derive substantial benefit from this technology. This highly selected patient group should exhibit symptoms requiring objective evidence of important reduction of quality of life either as measured by 6MWT or by repeated hospitalizations, but who nevertheless have at least a 1 year expected survival.

This number of patients should not exceed 5-6 per year.

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