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Scientific Update™

Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure: The COMPANION Trial

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The initial, preliminary results of the COMParison of medicAl therapy, paciNg, and defibrillatION in heart failure (COMPANION) trial indicate clinically and scientifically important benefits from biventricular pacing, as well as biventricular pacing plus automatic defibrillation, compared to pharmacologic therapy alone, in patients with severe left ventricular dysfunction and heart failure. There was an overall 19% reduction in all-cause mortality and all-cause hospitalizations in patients implanted with biventricular pacemakers, and a 19% reduction in combined all-cause mortality and all-cause hospitalization in patients implanted with biventricular pacing plus defibrillator devices. There was also a 43% reduction in all-cause mortality in heart failure patients receiving the combined pacing and defibrillation device.

Dealing with the high mortality in patients with chronic congestive heart failure (CHF) remains an important problem. Despite a decade of advances in the pharmacotherapy of patients with severe left ventricular dysfunction and clinical heart failure,(eg, beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) therapy, or spironolactone), the mortality in patients with advanced CHF remains quite high. In particular, mortality in patients with a prolonged QRS duration may be as high as 20% per year.

A decade of clinical trials has demonstrated that in patients with ischemic cardiomyopathy and very poor ventricular function (but not necessarily heart failure symptoms), implanted cardioverter defibrillators (ICDs) reduce mortality compared to no device therapy, by preventing arrhythmic death.[1,2] In patients with *symptomatic* heart failure, poor ventricular function, as well as QRS prolongation, therapy is directed towards improving cardiac function. Biventricular pacing, also known as cardiac resynchronization therapy (CRT) – the simultaneous pacing of the right ventricular apex and left lateral ventricle using a pacemaker lead inserted transvenously in a coronary sinus tributary – has been demonstrated to improve symptomatic status and objective measures of cardiac function up to 6 months following the device implantation.[3,4] To date, there has been no clear evidence that biventricular pacing by itself prolongs life and there have been no randomized clinical trials comparing CRT to CRT plus ICD (CRT-D) in the same device, compared to optimal pharmacological therapy (OPT).

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The COMPANION Trial

The hypothesis of the COMPANION study was that, in patients with advanced heart failure and QRS prolongation receiving optimal pharmacological therapy, biventricular pacing therapy would decrease the combined endpoint of hospitalization and all-cause mortality compared to no device therapy, and secondarily, that the combination of biventricular pacing and defibrillation in the same device would decrease hospitalization and all-cause mortality.[5] Eligible patients were randomized to 1 of 3 treatment arms:

- OPT,
- OPT plus CRT; and
- OPT plus the combined CRT-D.

Patients were stratified by beta-blocker use (which was not randomly allocated) and by investigational site; there was a 2-day window between randomization and implantation.

The primary endpoint was counted as time to death from any cause, or time to hospitalization for any reason. The hospital admission for the performance of the original surgical procedure in patients randomized to 1 of the 2 device arms was not counted in this primary endpoint (see below). A transient admission for >4 hours because of heart failure symptoms, if requiring IV inotropic therapy, was counted as a hospitalization for the purpose of the primary endpoint.

By prior intention, the single outcome of heart failure hospitalizations alone, and all-cause mortality alone were to be secondary endpoints.

Patient selection

Inclusion criteria were New York Heart Association (NYHA) class III or IV heart failure symptoms; sinus rhythm with QRS ≥120 msec and PR interval >150 msec; LVEF ≤35% and ventricular dilatation with end-diastolic diameter ≥60 mm; OPT (unless not tolerated) with a beta-blocker (for at least 3 months), diuretic, ACE inhibitor or ARB, and spironolactone and a history of heart failure hospitalization in the previous 12 months, but not within the last month.

Therapy was open-label. Events were to be counted from the day of randomization, except for the hospitalization event associated with surgery, which was not counted.

The sample size was calculated to yield a 90% power to detect a 25% reduction in the primary endpoint, from a 40% event rate over 12 months in the OPT group to 30% in either treatment group. One thousand events were expected in order for this power to be achieved, and the projected enrolment was 2200 patients.

Table 1: Selected baseline characteristics (total randomized, n = 1520)

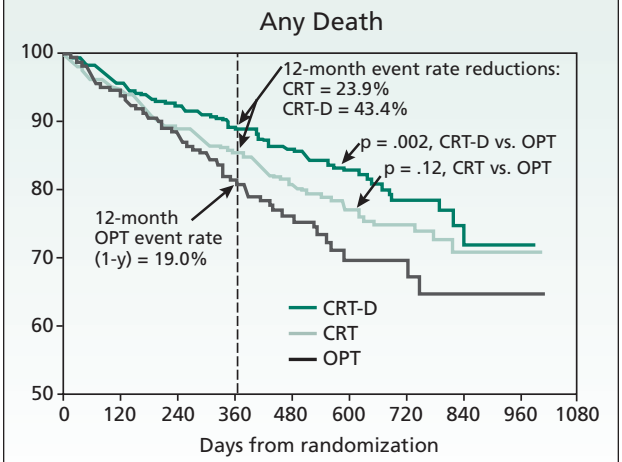
Parameter	A. OPT N = 308	B. CRT N = 617	C. CRT-D N = 595	P Values A/B, A/C
Age (years)	67	65	66	0.12, 0.14
Male gender (%)	69	67	67	0.70, 0.73
NYHA Class III (%)	82	87	86	.047, 0.12
Duration of HF (mos)	4.9	4.8	4.4	0.97, 0.44
LVEF (%)	22.8	22.0	22.5	0.08, 0.47
QRS duration (ms)	156	159	159	0.17, 0.11
Ischemic CMY	59	54	55	0.16, 0.23
LBBB (%)	70	69	73	0.84, 0.23
RBBB (%)	9	12	10	0.10, 0.48
ACEI (%) (or ARB)	69 (89)	70 (89)	68 (90)	0.75, 0.90 (0.93, 0.66)
Beta-blocker (%)	66	68	68	0.54, 0.69
Spironolactone	55	53	55	0.69, 0.94

OPT = optimal pharmacological therapy
CRT = cardiac resynchronization therapy (biventricular pacing)
CRT-D = CRT plus implanted cardioverter defibrillator

With respect to the secondary endpoint of all-cause mortality, there was an expected 24% mortality over 12 months with OPT and the study had an 80% power to detect a 25% reduction with either treatment in all-cause mortality.

A total of 1634 patients at 128 centres in the United States were enrolled in this study. On November 21, 2002, the study's Executive Committee halted enrolment in the trial following advice from the independent Data and Safety Monitoring Board that the pre-specified number of events for the study primary endpoints had been achieved. Dr. Bristow emphasized that the data, as presented, were not entirely complete and that additional data had to be collected and verified before the complete, fully adjudicated and verified study results could be analyzed. He nevertheless suggested that the

Figure 1: Secondary endpoint of all-cause mortality.



OPT = optimal pharmacologic therapy
CRT = cardiac resynchronization therapy (biventricular pacing)
CRT-D = CRT plus an implanted cardioverter defibrillator (ICD)

final results were most unlikely to be substantively different from those presented. Since 13% of the patients on OPT were withdrawn, complete follow-up will require re-consenting of these withdrawn patients to complete follow-up.

Results

Baseline characteristics in the 3 groups were well-matched (Table 1). At baseline, patients averaged approximately 66 years of age, 67% were male, and 86% were in NYHA class III. The mean LVEF fraction was approximately 22% and the mean QRS duration 160 msec. There was a relatively even split between ischemic and non-ischemic cardiomyopathy and the vast majority of patients were receiving OPT for heart failure.

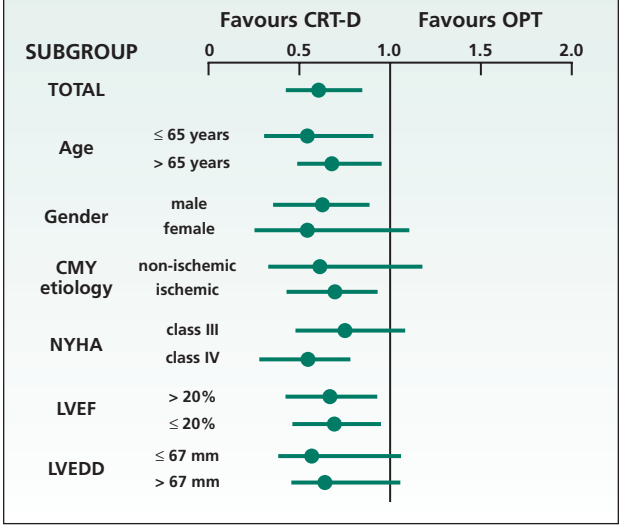
Primary endpoint

Patients receiving OPT had a 68% event rate at 1 year, with a 19% death rate and the remaining events being hospitalization for any cause or > 4 hours of IV inotropic therapy. In the CRT and in the CRT-D groups, there was a reduction of 35% and 39%, respectively, in this primary endpoint.

Secondary endpoints

Death or heart failure hospitalizations were similarly reduced, (from 46.1% in the OPT group) by 35.8% and

Figure 2: Subgroup hazard ratios (CRTD vs. OPT), mortality



CMY = cardiomyopathy
NYHA = New York Heart Association
LVEF = Left ventricular ejection fraction
LVEDD = Left ventricular end-diastolic diameter

39.5% in the CRT and the CRT-D groups, respectively, at 1 year. With respect to mortality, there was a significant reduction (p=.002) in all-cause mortality in patients who received CRT-D and a nonsignificant trend towards a reduction in all-cause mortality (p=0.12) in the CRT only group (Figure 1). Therefore, the 19% one-year overall death rate with OPT was reduced by 24% in the CRT group and 43% in the CRT-D group.

Examining all medically relevant subgroups, there were no apparent subgroup effects on mortality; the hazard ratio for mortality in all the CRT-D subgroups was to the left of the unity line (Figure 2).

With respect to complications, there was a 90% implantation success rate, with a mean duration of implant of 3 hours and 20 minutes. Moderate to severe adverse events occurred in 5% to 10% of device-treated patients.

Conclusions

The final study results are not available at the time of writing and will need to be reviewed carefully when all adjudicated endpoints are complete and the final analysis has been performed. Nevertheless, this study presents some very important evidence to confirm the previously documented

mortality benefit of implanted defibrillators and suggests, but does not prove, that the addition of biventricular pacing contributes to treatment benefit. The MADIT II study of ICDs for primary prevention in patients with coronary artery disease suggested that ICDs without CRT prolonged life, but led to increased heart failure hospitalizations.[6] In contrast, the combination of an ICD with CRT (CRT-D), in patients such as those studied in this trial, led to a statistically significant and clinically important reduction in both mortality and re-hospitalization. The small and statistically nonsignificant benefit of CRT alone on mortality is consistent with the approximately 20% reduction in mortality observed in the meta-analysis of CRT trials previously published.[4]

It is not possible, from these preliminary data, to clearly separate the benefits of CRT alone versus CRT-D. Pacing alone produces symptomatic benefit and reduces hospitalization, but would not be expected to have a major impact on cardiac arrhythmia mortality, except perhaps indirectly by reducing the propensity to cardiac arrhythmias with improvements in ventricular function. However, it is possible that biventricular pacing will independently reduce heart failure mortality.

Important limitations of this study include the "discounting" of the original hospitalization for patients randomized to device therapy. This meant that a prolonged hospitalization for complications relating to device implantation, or a heart failure hospitalization in the device group that was continuous or contiguous with the initial device hospitalization, would not be counted. Further data are awaited to resolve these ambiguities.

Nevertheless, this study represents an important advance in our understanding of the potential benefits of implanted devices as prophylaxis for all-cause mortality and heart failure hospitalization in patients with serious left ventricular dysfunction, symptomatic heart failure, and QRS prolongation. Completely consistent with previous information on defibrillators as primary prophylaxis, it seems reasonable that patients fulfilling the inclusion criteria for COMPANION should receive an ICD. It is not yet clear how much extra benefit the CRT provides, although this study documents a benefit similar to previously published studies, which indicated that at least for the intermediate term (up to 1 year), CRT reduces the requirement for heart failure re-hospitalization, and results in an improvement in cardiac symptoms. The COMPANION study did examine quality of life and other symptomatic endpoints for heart failure, and we eagerly await the details of these secondary endpoints.

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