CLINICAL TRIAL HIGHLIGHTS

SUP2 Trial: Selection Algorithm Benefits Patients With Recurrent Reflex Syncope

Written by Emma Hitt Nichols, PhD

Conducting a testing algorithm of patients with severe, recurrent, unpredictable syncope to receive a dual-chamber (DDD) pacemaker provides clinical benefit by reducing syncopal recurrence. Michele Brignole, MD, Ospedali del Tigullio, Lavagna, Italy, presented data from the prospective, observational SUP2 trial [Brignole M et al. *Eur Heart J*. 2015].

It is not yet established whether cardiac pacing with an implanted DDD pacemaker is beneficial in patients with reflex syncope. The purpose of the SUP2 trial was to determine if DDD pacemaker implantation is effective in reducing recurrent reflex syncope in patients with severe, recurrent, unpredictable cardioinhibitory (CI) reflex syncope.

The primary end point was to evaluate the efficacy of the diagnostic algorithm by measuring the time to first syncopal recurrence. Patients were enrolled if they were aged > 40 years and had severe, recurrent, unpredictable syncopes, which included CI carotid sinus syncope (CSS), Vasovagal Syncope International Study (VASIS) 2B response, or type 1 asystole. The algorithm began with cardiac sinus massage to detect CSS; if negative, patients underwent tilt testing for VASIS 2B response, and if this was negative, patients received an implantable loop recorder (ILR) to detect asystole. Patients positive for any of the above received pacing; all other patients were followed clinically.

Severe syncope was defined as unpredictable with or without short (< 10 seconds) prodromes that affected quality of life. Recurrent syncope was defined as ≥ 2 episodes within the past year or ≥ 3 episodes during the past 2 years. Suspected reflex syncope was defined as reflex syncope without severe structural heart disease, severe abnormalities, rhythm disturbances, orthostatic hypotension, and nonsyncopal causes of transient loss of consciousness.

After algorithm testing, 66 of 253 had CI CSS, 34 of the remaining 185 had a VASIS 2B response, and 25 of the remaining 134 had type 1 asystole, all of whom received a DDD pacemaker. Thus, in total, 125 out of 253 patients (47%) finally received a pacemaker. Among those who did not receive a pacemaker, 10 were lost to follow-up, 82 were ongoing with clinical observation, 4 had tachyarrhythmia, and 13 had no rhythm variations. At baseline, the mean age was 70 years, mean age of first syncope was 61 years, and the proportion of syncopes without or with prodromes < 10 seconds was 89%.

DDD pacemaker implantation was associated with significantly greater survival rates compared with patients who received only an ILR (15% vs 37% at 24 months; $P = .004$). DDD was not particularly more efficacious in any specific indication subgroup.

Prof Brignole highlighted that the data suggest that about 50% of patients with severe recurrent syncope have an asystolic reflex, and pacing resulted in a low recurrence rate. In conclusion, the SUP2 trial data indicate that using a testing algorithm to select patients who are candidates for pacing is feasible and provides clinical benefit.

Cardiac Implantable Electronic Devices Also Benefit Women, Sometimes More So

Written by Emma Hitt Nichols, PhD

The influence of sex on the beneficial effect of cardiac implantable electronic devices (CIEDs) has recently been appreciated, but remains poorly characterized. For example, implantable cardiac defibrillators (ICDs) may be less effective in women, whereas cardiac resynchronization therapy (CRT) defibrillators may be more effective. Importantly, women receive fewer implants than men in clinical practice and are underrepresented in clinical trials that evaluate CIEDs, making these questions difficult to answer.

Niraj Varma, MD, PhD, Cleveland Clinic, Cleveland, Ohio, USA, presented data from a retrospective study of sex-specific survival after a CIED implant. The purpose of the study was to use "big data" to characterize CIED utilization and postimplant mortality in women compared with men.

In this observational study, data from a cohort of 269 471 patients who received a CIED between 2008 and 2011 were evaluated for the primary outcome of all-cause mortality. CIEDs included pacemakers, ICDs, CRT pacemakers (CRT-P), and CRT defibrillators (CRT-D) from a single manufacturer. All devices were enabled with wireless remote monitoring, and all patients were followed for a minimum of 90 days. Patient demographics were accessed through the St Jude Medical device tracking database, and descriptive statistics were linked by patient ZIP code from the 2012 American Community Survey, which is administered by the US Census Bureau. Date of death was determined by the US Social Security Death Index Master File. The primary end point of all-cause survival was determined for each device type using unadjusted mortality incidence rates and adjusted Cox proportional hazards modeling stratified by age.

The mean age of the cohort was older than 70 years and two-thirds were men. Patients who received ICD implants were on average younger than patients implanted with other CIED devices. Across all device types, follow-up duration and remote monitoring utilization were comparable between sexes. The analysis revealed that a greater proportion of men received CIED implants across all device types. In particular, ICDs and CRT-Ds were implanted significantly less in women than in men. Survival was similar among men and women implanted with a pacemaker or ICD. Importantly, women who received CRT (CRT-D or CRT-P) experienced dramatically improved survival over men in the first 4 to 5 years post-CIED implant.

Dr Varma acknowledged that the limitations of this study included the limited clinical data available for a retrospective, observational analysis and the lack of a nondevice comparison group. However, he also noted that the strengths of the analysis were that it assessed a "real world" cohort of more than 200 000 patients and that it adds a large-scale evaluation of pacemaker and CRT-P patients.

Dr Varma concluded that this analysis suggests that women who receive a CRT-P or CRT-D have enhanced survival rates compared with men. In addition, women implanted with ICDs experienced similar survival rates as men. Therefore, strategies should be developed that ensure appropriate and full utilization of these devices in eligible women.

Micra Transcatheter Pacing System Safe, Effective

Written by Emma Hitt Nichols, PhD

The Micra Transcatheter Pacing System (TPS)—which is about 10-fold smaller than the conventional pacemaker and is implanted from the femoral vein and fixed in the right ventricle—was safe and effective in a range of patients who required ventricular pacing. Philippe Ritter, MD, Hospital Haut-Lévèque, Pessac, France, presented data from the Micra Transcatheter Pacing Study [Ritter P et al. *Eur Heart J*. 2015].

Currently, the only treatment for symptomatic bradycardia is permanent cardiac pacing. However, transvenous pacing systems may result in serious adverse events (AEs) in up to 12.4% of patients [Udo EO et al. *Heart Rhythm*. 2012]. The purpose of this study was to determine if the Micra TPS was effective and resulted in fewer serious AEs.

In this international phase 3 trial, patients with a class I or II indication for ventricular pacing [Epstein AE et al. *Heart Rhythm*. 2008] received the Micra TPS system. The Micra TPS system is about 10 times smaller than the conventional pacemaker and consists of an intracardiac accelerometer with flexible tines. At baseline, the median age was 78 years; 61% were men; and the median body mass index was 26 kg/m^2. In addition, 65% were diagnosed with bradycardia with permanent or persistent atrial tachyarrhythmia or atrial fibrillation; 16% had sinus node dysfunction; 14% had atrioventricular block; and 6% had another indication.

The primary safety end point was freedom from major Micra TPS–associated complications or procedures in the 6 months following implantation. The primary efficacy end point was a low and stable pacemaker threshold at 6 months. This analysis of 6-month outcomes included data from 140 patients, and analyses using longer term outcomes are planned.

The mean implantation time was 37 minutes, and the success rate was 100%. The Micra TPS implant was placed within the apex in 77% of patients, in the septum in 16%, in the midseptum in 6%, and in the right ventricular outflow tract in 1%. The median deployment per patient was 1, with successful first deployment in 59%, success achieved within 2 deployments in 81%, and success achieved within 4 deployments in 96%.

The serious AE rate was 5.7%, and 1.4% of patients required prolonged hospitalization; however, there were no device telemetry issues, dislodgements, infections, reoperations, or device-related deaths. Serious AEs included transient atrioventricular block, right bundle branch block, ventricular tachycardia, and ventricular fibrillation (Table 1).