Heart Rhythm UK

The SHTAC assessment report addresses both clinical and cost-effectiveness of ICD and CRT therapy in the groups of patients identified in the NICE scope – (i) people at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment (OPT), (ii) people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment (OPT) and (iii) people with both conditions. The Heart Rhythm UK submission dealt primarily with clinical effectiveness.

The conclusions of the SHTAC document are closely aligned with those of Heart Rhythm UK, as would be expected with both drawing on the same published clinical trial data, although there are some areas where interpretations differ.

1) *The addition of ICD to OPT was cost-effective at a WTP threshold of £30,000 for all of the scenarios modelled: previous ventricular arrhythmias/cardiac arrest, myocardial infarction more than 3 weeks previously, non-ischaemic cardiomyopathy, and ischaemic or non-ischaemic congestive heart failure and LVEF 35% or less; and in some cases at a WTP threshold of £20,000*.
   This is consistent with our conclusions that ICD therapy is appropriate for secondary prevention of life-threatening ventricular arrhythmias, and those with severe left ventricular impairment (LVEF ≤35% on echocardiography) regardless of aetiology.
2) *Both CRT-P and CRT-D presented an ICER below £30,000 per QALY gained compared with OPT, as did the comparison of CRT-D with CRT-P in people with heart failure as a result of LVSD and cardiac dyssynchrony*.
   This is consistent with our conclusions that patients with severe left ventricular impairment (LVEF ≤35%), evidence of dyssynchrony on ECG (QRS ≥120ms) and heart failure symptoms despite optimal pharmacological therapy benefit from CRT with improved symptoms, reduced hospitalisation and reduced all-cause mortality.
3) *In people with both conditions, the ICER for the comparison of CRT-D + OPT with ICD + OPT was below £30,000 per QALY (unless no difference in all-cause mortality was assumed) but not for the comparison with initial management with OPT alone. The costs and QALYs for CRT-D and CRT-P were similar*.
   The SHTAC analysis is consistent with the Heart Rhythm UK assessment that CRT-D is clinically effective in this group. However, the SHTAC conclusion on cost-effectiveness appears to be counter-intuitive. The clinical event rate for the end-points of arrhythmias and heart failure events is higher in those with both increased risk of sudden cardiac death and heart failure due to left ventricular systolic dysfunction, than in those without an increased risk of sudden cardiac death. If CRT-D is cost-effective compared to OPT in group 2, it is difficult to envisage a scenario where it would not be cost-effective in group 3. We would suggest a re-examination of the assumptions behind these calculations.

We are concerned that the groups described in the scope have not been defined by clinical criteria in the SHTAC analysis. This makes it difficult to determine which clinical trial data should be considered for each group and to derive clinical selection criteria for the therapies being considered. We believe that the approach taken in the Heart Rhythm UK submission is more appropriate – describing patient characteristics which not only identify those with increased risk of sudden cardiac death and/or heart failure due to dyssynchrony but also identify patients who have been shown to benefit from ICD (group 1), CRT pacing (group 2) or both treatments (CRT-D, group 3).

We do not understand the proposed strategy of "initial management with OPT alone followed by device implantation and upgrades as necessary" (p374). It is part of routine clinical practice, international guidelines and the entry requirement for clinical trials that medical therapy is optimised before consideration of device therapy. Once this has been done, a decision on device therapy is required. The event indicating the necessity for implantation or upgrade is not defined in the text and this strategy has not been tested in a clinical trial. As a high proportion of clinical events in these groups of patients are fatal, we would be very concerned that many patients would not have the opportunity to benefit from device therapy.

We were very surprised by the decision to disregard the "UK device longevity estimates derived from NHS data of the Central Cardiac Audit Database (CCAD) on all implants with verified life status from 2000 to 2011 (≈40,000 implants)" because of "clinical advice that these estimates seem to be overestimated".

- **page 285, paragraph 4**
  "The methodology used by the manufacturers to estimate devices' longevity is commonly used; however, clinical advice indicated that these estimates seem to be overestimated."

Clearly this could have had a very significant effect on cost-effectiveness calculations, device hardware costs being the largest part of total NHS costs. We think the authors should have used the device longevity data provided by CCAD on contemporary NHS patients or provide robust evidence that this is incorrect.

The SHTAC analyses do not separately consider people with rare conditions resulting in heart failure or increased risk of sudden cardiac death. We support the approach taken in the Heart Rhythm UK submission of using the best available risk stratification for these groups. SHTAC did not consider the use of CRT for patients in atrial fibrillation. We support the conclusions in the Heart Rhythm UK submission that patients in atrial fibrillation show similar benefit from CRT to those in sinus rhythm providing a high proportion of biventricular stimulation is achieved by pharmacological or ablation therapy.

There appear to be some factual errors in the descriptions of the technologies and their clinical context which are important to clarify in order to prevent any misunderstanding.

- **page 15, paragraph 2**
  "One trial reporting hospitalisations found higher rates per 1000 months follow-up among people with ICDs (11.3 vs 9.4, p=0.09), with higher heart failure hospitalisations (19.9% vs 14.9%)." This appears to refer to the DAVID trial which demonstrated that specific dual chamber ICD programming, increasing right ventricular pacing, was associated with increased heart failure events. It did not show any effect of anti-tachycardia (ICD) therapy on heart failure. The results of this trial have altered routine clinical practice to avoid this effect.

- **page 14, paragraph 4**
  "People scheduled for CABG surgery: One RCT found no difference in all-cause mortality (RR 1.08, 95% CI, 0.85 to 1.38; p=0.53), total cardiac deaths (HR 0.97, 95% CI, 0.71 to 1.33, p=0.84), non-arrhythmic (HR 1.24, 95% CI, 0.84 to 1.84; p=0.28), non-cardiac death (RR 1.50, 95% CI, 0.82 to 2.73; p=0.19). Rates of SCD 16 were lower with ICD, but this did not reach statistical significance (HR 0.55, 95% CI, 0.29 to 1.03; p=0.06)." This appears to refer to the CABG-patch trial published in 1997. This used selection criteria (signal averaged ECG) which have not been shown to be appropriate and are no longer part of clinical practice and the surgical implantation of epicardial patches for defibrillation which carried a high intra-operative mortality which have not been used in clinical practice for 20 years. This trial documents the history of ICD development but is not relevant to current ICD treatment in the UK. Its results should not be used to infer the clinical effectiveness or risk associated with current practice.

- **page 28, section 1.2**
  Cardiac rhythm devices do not function to prevent ventricular arrhythmias – they treat arrhythmias once they have occurred with low-voltage (up to 10V) rapid pacing (anti-tachycardia pacing, ATP) or high voltage (750V) defibrillation. Cardioversion is a term usually reserved for the restoration of sinus rhythm in a patient with an atrial arrhythmia and remains part of the nomenclature of ICDs for largely historical reasons.

- **page 29, paragraph 4**
  It is not clear to what the term "resynchronisation shocks" refers. In this context, resynchronisation refers to low-voltage pacing of the atria, left and right ventricles to improve cardiac efficiency. It is delivered to the chambers in a coordinated sequence to maximise synchronisation. It is designed to correct dyssynchrony, not arrhythmias. Ventricular arrhythmias

are treated by anti-tachycardia pacing or high voltage defibrillation shocks (as above). These affect the entire heart and cannot be confided to a specific chamber.

- **page 31, paragraph 3**
  There appears to have been a typographical error suggesting that an ICD (ventricular only, VVIR, or dual chamber, DDDR) is more expensive at £18,303, than a CRT-defibrillator (triple chamber, biventricular pacing) at £17,184. This is not the case – CRT-D devices are more complex and are always more expensive than dual or single chamber ICDs. We would be grateful if the authors check that these figures have not been used in error in their calculations.

- **page 32, paragraph 3**
  Blood samples are never routinely taken from within the heart to identify sudden cardiac death risk.

- **page 33, paragraph 4**
  Amiodarone and other rhythm modifying drugs are not used routinely as part of pharmacological therapy in patients at risk of SCD. They are reserved for specific indications as it is recognised that there is no evidence that they reduce mortality.

- **page 40, paragraph 2**
  There is a typographical error: "ICD, CRT-P and CRT-P" should read "ICD, CRT-P and CRT-**D**".

- **page 40, paragraph 5**
  The 3 groups defined in the scope – people at risk of sudden cardiac death (without heart failure and dyssynchrony), those with heart failure (without an increased risk of sudden cardiac death) and those with both conditions do not overlap by definition. We think a better description is that most affected people are in the 3rd group, with both problems.

- **page 62, paragraph 3**
  The manuscript states that "All participants in CASH[83] and DEBUT,[91] 90% in CIDs[86] and 60% in AVID[73] had congestive heart failure. The majority (approximately 87%) of people in CASH[83] had NYHA Class I or Class II heart failure, whereas about half those in AVID[73] and CIDS[86] fell into these categories. Almost 40% of participants in CIDS[86] had moderate to severe heart failure (NYHA Class III and IV), compared with 10% of people in AVID[73] and 16% (all NYHA Class III) of people in CASH.[83] Mean LVEF was higher in CASH[83] (46%) than in AVID[73] (32%) or CIDS[86] (34%), suggesting there may have been disproportionate representation of relatively healthy participants in CASH.[83]". However, these secondary prevention trials did not include only patients with heart failure. No patients in DEBUT had heart failure, 11% in CIDS were in NYHA III/IV heart failure, about 25% in CASH were asymptomatic (NYHA I) and the mean LVEF was 46% in ICD group and 47% in AAD group. We would suggest rechecking to ensure that this misconception has not resulted in the analysis of trial data against the incorrect group.