NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA314; Implantable cardioverter defibrillators and cardiac resynchronisation therapy (biventricular pacing)

Original publication date:	June 2014
Review date	May 2017
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA314, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Rationale

Overall, the new evidence identified was supportive of the existing recommendation. Cardiac resynchronisation therapy in patients with intermediate QRS intervals between 120 to 149 milliseconds was identified in TA314 as an area of uncertainty and this subgroup was not included in the recommendation. New evidence relating to this group was in line with the evidence base considered for TA314 and supports the existing recommendations.

The companies have confirmed that no changes in marketing authorisation are anticipated and were not aware of any new evidence that would change the existing recommendations. There are some newer versions of these devices (for example with longer life batteries, remote monitoring or wireless technology) that were not available at the time of TA314. Many of these are covered by NICE medical technologies guidance (see Appendix C).

It is therefore proposed that TA314 is moved to the static list because no evidence has been identified that is likely to alter the conclusions of the guidance (that is, lead to a change in the clinical and cost effectiveness of implantable cardiac defibrillators and cardiac resynchronisation therapy).

3. Summary of new evidence and implications for review

The search strategy from the original Assessment Report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from November 2012 onwards were reviewed. Additional searches of clinical trials

registries and other sources were also carried out. The results of the literature search are discussed below. See Appendix C for further details of ongoing and unpublished studies.

TA314 compared implantable cardioverter defibrillators and cardiac resynchronisation therapy to treat arrhythmias and heart failure. In TA314 there was a lack of evidence on the use of cardiac resynchronisation therapy in patients with intermediate QRS intervals (120 to 149 milliseconds). The committee considered an individual patient level meta-analysis (Cleland et al 2013) that showed the clinical benefit was smaller and more uncertain, with a potentially harmful effect in this subgroup. Since the publication of TA314, more recent systematic reviews and meta-analyses also show similar findings to Cleland et al (2013). The new evidence supports the conclusions in TA314 and additional analyses would be unlikely to change the original recommendations. A summary of the new evidence is presented in the table below.

Has there been any change to the price of the technologies since the guidance was published?
Individual companies have provided updated costs for their devices, the average cost to the NHS of these devices may have changed since TA314. However, in TA314 the price of the devices was not a main driver of the cost effectiveness model, therefore it is unlikely that this would change the existing recommendations.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There are no proposed changes to the marketing authorisation that would affect the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
In TA314 there was a lack of RCT evidence for the use of cardiac resynchronisation therapy in patients with intermediate QRS intervals (120 to 149 milliseconds). The committee considered an individual patient level meta-analysis (Cleland et al 2013) that showed the clinical benefit of cardiac resynchronisation therapy in patients with QRS durations between 120 and 140 milliseconds was smaller and less certain than those with a longer QRS duration. The meta-analysis also found that cardiac resynchronisation therapy could have a potentially harmful effect in patients with a QRS duration of less than 126 milliseconds. This subgroup was not included within the recommendation for cardiac resynchronisation Since TA314 was published in 2014, at least 2 systematic reviews with meta-analyses (Wang et al 2015, Shah et al 2015) examine the effect of cardiac resynchronisation therapy in patients with narrow QRS intervals. These recent reviews also show that cardiac resynchronisation therapy does not improve

clinical benefit in patients with a narrow QRS intervals (less than 130 milliseconds) and can be associated with potentially harmful effects.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance. CG108 Chronic heart failure in adults: management is currently being updated with an anticipated publication date in August 2018. The existing guideline makes a cross-reference to TA95 (updated and replaced by TA314). The scope for this update states that referral for implantable cardiac defibrillators would be removed from the final guidance. Therefore the update of CG108 will not include an updated evidence review for implantable cardiac defibrillators and may cross refer to TA314. The update will also include an evidence review on the criteria for guiding defibrillator deactivation: it is not expected that this will conflict with existing technology appraisals guidance.
Additional comments
It has been raised by a stakeholder that implanting devices is associated with significant mortality and that some patients may not benefit. There may therefore be value in creating risk scores for individual groups of patients, which cost effectiveness could be based upon. Creating a risk scoring system would be beyond the remit of a technology appraisal. Should a scoring system already exist, this challenge may also be better addressed through clinical consideration rather than cost effectiveness analyses.

4. Equalities issues

No equality issues were raised during TA314 that were relevant to the committee's recommendations.

GE paper sign off: **Meindert Boysen, 9 May 2017**

Contributors to this paper:

Information Specialist: Tom Hudson

Technical Analyst: Abi Senthinathan

Associate Director: Melinda Goodall

Project Manager: Samantha Shannon

CCP input: Ben Doak

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of: implantable cardioverter defibrillators in the treatment of arrhythmias and biventricular pacing (cardiac resynchronisation) to restore synchronous cardiac contraction in patients with advanced heart failure.

6. Current guidance

1.1 Implantable cardioverter defibrillators (ICDs) are recommended as options for:

- treating people with previous serious ventricular arrhythmia, that is, people who, without a treatable cause:
    - have survived a cardiac arrest caused by either ventricular tachycardia (VT) or ventricular fibrillation or
    - have spontaneous sustained VT causing syncope or significant haemodynamic compromise or
    - have sustained VT without syncope or cardiac arrest, and also have an associated reduction in left ventricular ejection fraction (LVEF) of 35% or less but their symptoms are no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.
- treating people who:
    - have a familial cardiac condition with a high risk of sudden death, such as long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome or arrhythmogenic right ventricular dysplasia or
    - have undergone surgical repair of congenital heart disease.

1.2 Implantable cardioverter defibrillators (ICDs), cardiac resynchronisation therapy (CRT) with defibrillator (CRT-D) or CRT with pacing (CRT-P) are recommended as treatment options for people with heart failure who have left ventricular dysfunction with a left ventricular ejection fraction (LVEF) of 35% or less as specified in table 1.

Table 1 Treatment options with ICD or CRT for people with heart failure who have left ventricular dysfunction with an LVEF of 35% or less (according to NYHA class, QRS duration and presence of LBBB)

	NYHA class			
QRS interval	**I**	**II**	**III**	**IV**
<120 milliseconds	**ICD if there is a high risk of sudden cardiac death**			**ICD and CRT not clinically indicated**
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P
LBBB, left bundle branch block; NYHA, New York Heart Association				

7. Research recommendations from original guidance

Not applicable.

8. Cost information from original guidance

3.1 to 3.3 Based on average selling prices aggregated across all manufacturers of implantable cardioverter defibrillators sold in the UK to the NHS in the financial year of 2011, the cost of a complete implantable cardioverter defibrillator system was estimated at £9692. The cost of a complete cardiac resynchronisation therapy with pacing system is estimated to be £3411 and the cost of a complete cardiac resynchronisation therapy with a defibrillator system is estimated to be £12,293.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Chronic heart failure in adults: management (2010) NICE guideline CG108

Chronic heart failure in adults (2011 updated 2016) NICE quality standard 9

Insertion of a subcutaneous implantable cardioverter defibrillator for prevention of sudden cardiac death (2013) NICE interventional procedures guidance 454

ENDURALIFE powered CRT-D devices for treating heart failure (2017) NICE Medical technologies guidance MTG33

LATITUDE NXT Patient Management System for monitoring cardiac devices at home (2016) NICE medtech innovation briefing 67

CareLink network service for remote monitoring of people with cardiac devices(2016) NICE medtech innovation briefing 64

In progress

Chronic heart failure in adults: management NICE guideline. Publication expected: August 2018

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Autologous stem cell therapy (Ceylad)	Phase III for treating chronic heart failure after ischaemic cardiomyopathy	Yes

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Implantable cardioverter defibrillators (ICDs) are small, battery-powered devices that are implanted under the skin just below the collarbone, with leads (tiny wires) inserted into the heart. The devices operate by	Indication: No change in intended use of device

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
sensing and analysing the electrical activity of the heart, thereby monitoring for arrhythmia, and delivering electrical pulses or shocks to restore normal rhythm if necessary. Based on average selling prices aggregated across all manufacturers of ICDs sold in the UK to the NHS in the financial year of 2011, the cost of a complete ICD system was estimated at £9,692.	Source: Biotronik, Boston Scientific, EBR systems, Liva Nova and Medronic Cost: No average cost of ICD devices across the NHS
Cardiac resynchronisation therapy with pacing (CRT-P), also known as biventricular pacing, involves implanting a pulse generator in the upper chest. Three leads connect this to the right atrium and both ventricles, and the device resynchronises the contraction of the ventricles, thereby improving the heart's pumping efficiency. Based on average selling prices aggregated from devices sold in the UK to the NHS across all manufacturers in the financial year of 2011, the cost of a complete CRT-P system is estimated to be £3,411.	Indication: No change in intended use of device Source: Biotronik, Boston Scientific, EBR systems, Liva Nova and Medronic Cost: No average cost of CRT-P devices across the NHS
Cardiac resynchronisation therapy with a defibrillator device (CRT-D) combines CRT-P and ICD devices. A CRT-D device defibrillates the heart internally in the event of an acute arrhythmic event and improves ventricular efficiency and blood flow. Based on average selling prices aggregated from devices sold in the UK to the NHS across all manufacturers in the financial year of 2011, the cost of a complete CRT-D system is estimated to be £12,293.	Indication: No change in intended use of device Source: Biotronik, Boston Scientific, EBR systems, Liva Nova and Medronic Cost: No average cost of CRT-D devices across the NHS

4. Registered and unpublished trials

Trial name and registration number	Details
Efficacy of Implantable Defibrillator Therapy After a Myocardial Infarction (REFINE-ICD) NCT00673842; 21721	ICD vs. no ICD in in people who have had a heart attack in the prior 5 years, have abnormal test results from a 24 hour heart monitor, and who have low normal heart function. n = 1000 Estimated primary completion date: January 2019 Estimated overall completion date: December 2021
Atrioventricular Junction Ablation and Biventricular Pacing for Atrial Fibrillation and Heart Failure NCT02137187; CPMCV-01-14	Drug therapy + ICD vs. ablation + CRT-P or CRT-D n = 1830 Estimated primary completion date: May 2017 Estimated overall completion date: May 2019
Utility of Tissue Doppler Echocardiography for Selecting Patients for Cardiac Resynchronisation Therapy NCT01100918; 004844BLT	3 arm trial. Participants without dyssynchrony are randomised to CRT-D or ICD only. n = 80 Estimated overall completion date: December 2010
Assessment of Cardiac Resynchronization Therapy in Patients With Wide QRS and Non-specific Intraventricular Conduction Delay: a Randomized Trial NCT02454439; CHU-0233; 2014-A01848-39	Participants given CRT or CRT-D, then randomised to device on-or-off. n = 200 Estimated primary completion date: May 2018 Estimated overall completion date: November 2018
Implantable Cardioverter Defibrillator Versus Optimal Medical Therapy In Patients With Variant Angina Manifesting as Aborted Sudden Cardiac Death NCT02845531; AMCCV2016-15; VARIANT-ICD	n = 140 Estimated primary completion date: December 2022 Estimated overall completion date: June 2023

Trial name and registration number	Details
Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients NCT02922036; CSP-03035; SOLVE-CRT	WiSE (CRT) system on-or-off n = 350 Estimated primary completion date: September 2019 Estimated overall completion date: September 2020
Atrioventricular Node Ablation in Patients With Atrial Fibrillation and Moderate Chronic Heart Failure NCT01512381; zubarev-vista-17-12; VISTA	CRT vs. conventional pacemaker n = 60 Estimated primary completion date: May 2017 Estimated overall completion date: December 2017
Atrial Fibrillation Ablation Compared to Rate Control Strategy in Patients With Impaired Left Ventricular Function NCT02509754; AFARC-LVF; FG062015TRN	Ablation + ICD vs. ICD or CRT-D n = 180 Estimated primary completion date: June 2017 Estimated overall completion date: December 2017
The His optimised pacing evaluated for heart failure trial ISRCTN86179285; HOPE - HF	Participants randomised to pacemaker or ICD vs. no pacing n = 160 Estimated overall completion date: October 2019

5. Relevant services covered by NHS England specialised commissioning

A specialist clinical reference group on cardiothoracic services covers ICD and CRT use. NHS England published a service specification for ICD and CRT services in 2013.

Appendix D – References

Cleland JG, Abraham WT, Linde C, et al (2013). An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. European heart journal 34 (46), 3547-56.

Shah R M, Patel D, Molnar J et al (2015) Cardiac-resynchronization therapy in patients with systolic heart failure and QRS interval <130 ms: insights from a meta-analysis. Europace: Journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 17(2), 267-73.

Wang G, Zhao Z, Zhao S et al (2015) Effect of cardiac resynchronization therapy on patients with heart failure and narrow QRS complexes: a meta-analysis of five randomized controlled trials. Journal of interventional cardiac electrophysiology 44(1), 71-9.