NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of 152; Drug-eluting stents for the treatment of coronary artery disease

This guidance was issued in July 2008.

The review date for this guidance was June 2012. The review was deferred at this time to allow for further information gathering.

1. Recommendation

The guidance should be updated in a forthcoming guideline. That we consult on this proposal.

2. Original remit(s)

“As part of the planned review of guidance on coronary artery stents, to appraise the clinical and cost effectiveness of drug eluting stents compared with conventional stents for the primary prevention of restenosis following percutaneous transluminal coronary angioplasty”.

3. Current guidance

1.1. Drug-eluting stents are recommended for use in percutaneous coronary intervention for the treatment of coronary artery disease, within their instructions for use, only if:

- the target artery to be treated has less than a 3-mm calibre or the lesion is longer than 15 mm, and
- the price difference between drug-eluting stents and bare-metal stents is no more than £300.

4. Rationale[1]

The systematic literature review indicates that treatment of coronary heart disease with stents remains a highly active area of research, and a substantial volume of new evidence and numerous new technologies have emerged since the publication of TA152; in particular, a number of comparisons between different DESs, and comparisons between DESs and bare-metal stents (BMSs), in part with consistent results. However, there is no strong evidence that the key factors on which the current recommendations and the economic models depend would change if a technology appraisal review was carried out. Furthermore, differentiation between all

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

available stents would not be possible based on the currently available evidence. Because of the locally negotiated prices, a recommendation based on local costs remains appropriate and is unlikely to be phrased substantially differently. It is acknowledged that further assessment of these technologies, and in particular the stents that have become available since publication of the original guidance, might potentially be helpful for clinicians. However, a technology appraisal is not an appropriate tool for such an assessment. It is therefore proposed that the guidance should be updated in a forthcoming clinical guideline.

5. Implications for other guidance producing programmes

It is most useful if the recommendations in TA152 are updated in the forthcoming updates to the STEMI and NSTEMI guidelines. The reviews of CG167 on STEMI is scheduled to be start in July 2015, and of CG94 on NSTEMI in September 2015.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from April 2010 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The systematic literature searches identified a large quantity of new evidence relevant to the appraisal of drug-eluting stents (DESs). This includes a number of systematic reviews, meta-analyses, randomised controlled trials and observational studies (for example registries). In particular, the evidence provides a number of comparisons between different DESs, and comparisons between DESs and bare-metal stents (BMSs). Key aspects of the new evidence that may be relevant to the current review are explored below, illustrated with examples; it should be noted that the current document does not aim to summarise all studies identified in the literature searches.

DES versus DES

The Committee for TA152 identified ongoing head-to-head comparisons between DESs as an important research need, and several such studies have now been performed. Overall, the results appear equivocal: although some studies identified statistically significant differences between DESs, others demonstrated non-inferiority or no statistically significant differences. For example:

- No clinically important differences were observed in comparisons between sirolimus- and paclitaxel-eluting stents, sirolimus- and everolimus-eluting stents, or everolimus- and biolimus-eluting stents (Cassese et al. 2013; Jensen et al. 2012; Smits et al. 2013).
- Most comparisons between everolimus- and paclitaxel-eluting stents indicated that everolimus-eluting stents gave superior outcomes (Alazzoni et al. 2012; Bangalore et al. 2013a); however, some studies suggested that there were no

significant differences between these stents (De la Torre Hernandez JM et al. 2013).

- Similarly, mixed results were observed in studies comparing zotarolimus- and paclitaxel-eluting stents, zotarolimus- and sirolimus-eluting stents, and biolimus- and sirolimus-eluting stents. Where significant differences were observed, paclitaxel and sirolimus appeared superior to zotarolimus, and biolimus appeared superior to sirolimus (Fan et al. 2013; Gray et al. 2012; Serruys et al. 2013).
- A systematic review and meta-analysis (Wang et al. 2013) suggested that second-generation DESs are associated with decreased stent thrombosis but increased target lesion revascularisation, compared with first-generation DESs. There were no significant differences in major adverse cardiac events, all-cause death, cardiac death or recurrent myocardial infarction (MI).
- Studies have also examined potential differences between different DESs with the same eluted drug. Most studies found no significant differences between different paclitaxel-eluting stents, sirolimus-eluting stents or everolimus-eluting stents. Conversely, one study found differences in angiographic restenosis between 2 zotarolimus-eluting stents (Tada et al. 2013).
- No head-to-head studies involving tacrolimus-eluting, novolimus-eluting or tretinoin-eluting DESs were identified.

From this initial review of the evidence, it is clear that a full comparison of all currently available DESs would not be feasible to support detailed and robust and recommendations on the choice between DESs. Although a further assessment of this emerging evidence may be helpful for clinicians, a technology appraisal may not be the most appropriate tool for such an assessment.

DES versus BMS

Relatively few new studies were identified that compared DESs with BMSs. Of note, an analysis of the BASKET-PROVE randomised controlled trial indicated that DESs significantly reduced the risk of major adverse cardiac events compared with BMSs, in people with large arteries (Hansen et al. 2013).

Many of the identified comparisons between DESs and BMSs looked specifically at people with ST-segment elevation myocardial infarction (STEMI). Two meta-analyses indicated that sirolimus-, paclitaxel- and everolimus-eluting stents were associated with statistically significant decreases in the risk of target vessel revascularisation compared with BMSs (relative risk reduction 50–60%), with no increase in the risk of death, MI or stent thrombosis (Bangalore et al. 2013a; Luca et al. 2012). Similarly, the EXAMINATION trial comparing the everolimus-eluting Xience V stent with a cobalt–chromium BMS found a non-significant benefit for DESs in the primary endpoint of death, MI and repeat revascularisation. Statistically significant benefits were shown for the secondary endpoints of target vessel and lesion revascularisation and stent thrombosis (Sabate et al. 2012). Conversely, the 5-year results from the DEDICATION trial in people with STEMI showed non-significant differences between DESs and BMSs for major adverse cardiac events and all-cause mortality, but a higher rate of cardiac death among people treated with DESs (Holmvang et al. 2013).

Although the evidence available at the time of the previous appraisal included only a relatively small group of patients with STEMI, the recommendations apply to both elective and non-elective procedures. The most recent evidence appears broadly consistent with the evidence available at the time of the previous appraisal.

Emerging technologies: biodegradable stents and drug-coated balloons

Biodegradable stents and drug-coated balloons (DCBs) are technologies that were not explicitly considered during the appraisal of DESs, but which could potentially be relevant treatment options. A meta-analysis published by Bangalore et al. suggested that biodegradable stents may be superior to first-generation DESs but not to newer-generation durable stents (Bangalore et al. 2013b). Similarly, published results for DCBs are mixed. One meta-analysis suggested that DCBs may be similar in efficacy and safety to DESs (Lupi et al. 2013), while a second concluded that the efficacy of DCB is between that of BMSs and that of DESs (Frohlich et al. 2013). Conversely, a randomised comparison between a paclitaxel-coated balloon plus BMS and an everolimus DES was stopped early because of high revascularisation rates in the DCB + BMS group, with neointimal growth comparable with historical BMS data in this group (Liistro et al. 2013).

As for the comparison between DESs, the available evidence suggests that a full comparison of all currently available biodegradable stents, DCBs and DESs would not be feasible. It may be more appropriate for emerging stent technologies to be considered through an alternative NICE programme; one such technology has already been reviewed in the Medical Technologies Evaluation Programme (Medical technologies guidance 1, December 2010) [redacted].

Key factors affecting the cost effectiveness of DESs

The Assessment Group for TA152 identified 4 key variables affecting the outcome of its economic model: the acquisition costs of DESs (discussed in the section below), the number of stents used, the absolute risk of revascularisation with BMSs, and the reduction in the risk of revascularisation associated with DESs. In addition, longer-term factors, including the use of antiplatelet treatments and stent thrombosis, may affect the outcomes associated with BMSs and DESs. A number of studies identified as part of the current review provide additional evidence to inform these variables. For example:

- A meta-analyses conducted in people with STEMI suggested that the risk of revascularisation associated with BMSs was 20.1% (Luca et al. 2012). This finding is higher than the base-case estimate of 11% preferred by the Committee in TA152; however, the Committee noted at the time that many estimates from clinical trials were higher than would be seen in clinical practice, due to protocol-driven angiography.
- This same meta-analysis estimated the relative risk reduction associated with DESs to be approximately 40% – a little lower than the estimate preferred by the Committee (55% in the base case, 65% in a sensitivity analysis). Conversely, a second meta-analysis also conducted in people with STEMI estimated the relative risk reduction to be approximately 50–60% (Bangalore et al. 2013a), consistent with the estimates preferred by the Committee.

- Recommendations from the FDA and BCIS advise using extended clopidogrel therapy for people receiving DESs; no evidence has been identified to suggest that this guidance has changed. Two clinical studies have suggested that 6 months' anti-platelet therapy is non-inferior to 12 months' treatment (Crawford-Faucher 2012; Gwon et al. 2012). However, both of these studies, as well as a meta-analysis of 174 studies (Ba et al. 2012), emphasised the need for further research in this area.

It is possible that a review of the guidance could allow for development of more robust estimates of the key variables, although it is unlikely that the recommendations would change unless the preferred estimates changed substantially. It is not known at this stage whether there is sufficient high-quality evidence from real-world studies or disease registries to support a substantial change to the estimates of revascularisation or the duration of antiplatelet therapy.

Subgroups and specific situations

The recommendations in TA152 were restricted to specific lesion lengths and vessel diameters, and so consideration is given to the emerging evidence on these situations.

- A meta-analysis of 6 randomised controlled trials found that DESs were associated with a significant reduction in the risk of revascularisation compared with BMSs, in people with large vessels (Geng et al. 2013). Similarly, subgroup analyses of the TAXUS IV study indicated that the effect of DESs in reducing the risk of revascularisation was similar regardless of vessel diameter (Ellis et al. 2009). The absolute risk of target lesion revascularisation with BMSs was 60% higher in people with vessels less than 3 mm in diameter compared to those with wider vessels, confirming that small vessel diameter is an important risk factor for revascularisation.
- These 2 studies also indicated that the benefits of DESs remained consistent across different stent lengths (Ellis et al. 2009; Geng et al. 2013). The risk of target lesion revascularisation with BMSs did not differ between short and long lesions (less than 18 mm or 18 mm or more respectively) (Ellis et al. 2009). However, the risks observed in this study were substantially higher than the estimates preferred by the Committee, suggesting that the results may not be directly comparable.

The new evidence relating to the effects of vessel diameter and lesion length does not suggest that a more detailed review is necessary.

In addition, further evidence has been identified for a number of subgroups and situations that were not considered separately in TA152. These subgroups include people with diabetes, acute MI (including STEMI, as discussed above, and total vessel occlusions), bifurcating lesions and left main artery disease. It is notable that the Committee did not previously consider diabetes to be a separate risk factor for restenosis. Further review of the emerging evidence would be warranted only if specific recommendations for these subgroups are needed or if key factors affecting the economic model (e.g. the risk of revascularisation) differ substantially in these groups compared with the population as a whole.

Economic analyses

Six economic analyses evaluating the cost effectiveness of DESs or BMSs were identified (Amin et al. 2012; Baumler et al. 2012; Rodriguez et al. 2012; Turco et al. 2012; Willich et al. 2013; Wisloff et al. 2013). None of these considered the perspective of the NHS, and so the results are unlikely to impact on the recommendations of TA152.

Availability and costs of technologies

Of the 11 DESs included in TA152, 4 have been since been withdrawn (Appendix 2). However, the number of available DESs has grown substantially since the initial guidance. The original appraisal considered 11 DESs, eluting paclitaxel, sirolimus, zotarolimus, tacrolimus, everolimus and dexamethasone (of which 4 are no longer available, Appendix 2). A total of 27 new DESs have CE marks awarded or pending: 9 containing paclitaxel, 5 containing sirolimus, 5 containing everolimus, 4 containing biolimus, 2 containing zotarolimus, 1 containing tretinoin and 1 containing novolimus (Appendix 2). The availability and use of these stents in UK clinical practice is unknown. It is acknowledged that, strictly speaking, the recommendations in TA152 apply only to the stents that were named in that appraisal; as such, a review of the guidance might provide clarity for all of the stents that are available now. However, no evidence has been identified to suggest that this strict interpretation is leading to difficulties in accessing any of the more recently launched stents. Furthermore, it is unlikely that sufficient evidence is available for a full appraisal of all available products, and the continuous addition to the market of new stents may make any technology appraisal somewhat outdated very quickly.

The acquisition cost of stents was a key issue in TA152. It was noted during the appraisal that procurement of devices such as stents was complex, and the prices paid for them varied across the country depending on specific contract arrangements. Consequently, the final guidance recommended that DESs may be used only if the price difference between DESs and BMSs is no more than £300 There is no evidence that the pricing and procurement arrangements for stents have changed. Because of the locally negotiated prices, a recommendation based on local costs remains appropriate and is unlikely to be phrased substantially differently in any updated guidance.

Ongoing research

A large number of ongoing clinical trials has been identified: these are summarised in Appendix 2. These studies indicate that stent treatment for coronary heart disease remains a highly active area of research.

Implications for review

The systematic literature review indicates that treatment of coronary heart disease with stents remains a highly active area of research, with substantial amounts of evidence and numerous new technologies emerging since the publication of TA152. However, there is little strong evidence that the key factors on which the economic models depend would change dramatically if a review of the evidence were carried out. Furthermore, a full comparison between all currently available stents would not

be possible based on the currently available evidence; although additional assessment of the latest evidence may be helpful, a technology appraisal is not an appropriate tool in this instance. The use of a recommendation based on local costs remains appropriate and does not need to be reviewed.

8. Implementation

A submission from Implementation is included in Appendix 3. The information presented indicates that there has been a steady growth in both the number and proportion of people treated with DESs since the publication of TA152. The total number of procedures reached almost 58,000 finished consultant episodes in 2012/13. Audit evidence suggests that approximately 90% of people who undergo percutaneous coronary intervention receive a stent, and 70% of people receive a DES (2011); projections from 2009 suggested that 90–80% of people would receive a DES if NICE guidance were followed, suggesting that implementation of the guidance is good. Qualitative feedback emphasises that the NICE guidance has been valuable.

9. Equality issues

No relevant equality and diversity issues have been identified.

GE paper sign off: Elisabeth George, 21 Mar 2014

Contributors to this paper:

Information Specialist:	Tom Hudson
Technical Lead:	Ian Watson
Technical Advisor:	Jo Richardson
Implementation Analyst:	Rebecca Braithwaite
Project Manager:	Andrew Kenyon

Appendix 1 – 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.	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.	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
The guidance should be updated in an on-going/forthcoming clinical guideline.	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).	Yes

Options	Consequence	Selected – 'Yes/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.	No

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Ischaemic heart disease - coronary artery stents. Technology Appraisal TA71. Issued: October 2003. The recommendations in TA152 replace recommendations 1.2 – 1.4 in TA71. Sections 1.1 and 1.5 of technology appraisal TA71 remain extant and concern when the use of a stent should be considered.

Management of stable angina. Clinical Guideline CG126. Issued: July 2011. Anticipated review date: July 2014.

Quality standard for stable angina. QS21. Issued: August 2012.

Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. Clinical Guideline CG94. Issued: March 2010. Considered for review in March 2013 – not being updated at this time.

MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. Clinical Guideline CG172. Issued: November 2013.

Myocardial infarction with ST-segment elevation: The acute management of myocardial infarction with ST-segment elevation. Clinical Guideline CG167. Issued: July 2013.

SeQuent Please balloon catheter for in-stent coronary restenosis. Medical Technologies Guidance MTG1. Issued: February 2010.

Percutaneous laser coronary angioplasty. Interventional Procedure Guidance IPG378. Issued: January 2011.

Off-pump coronary artery bypass grafting. Interventional Procedure Guidance IPG377. Issued: January 2011.

Totally endoscopic robotically assisted coronary artery bypass grafting. Interventional Procedure Guidance IPG128. Issued: June 2005.

In progress

Optical coherence tomography to guide percutaneous coronary intervention. Interventional Procedure Guidance. Provisional publication date: Autumn 2013.

In topic selection

[redacted]

[redacted]**Details of changes to the indications of the technology**

Four drug-eluting stents referred to in the documentation for TA152 are no longer available. These are: Dexamet; Axxion; Cypher and Cypher Select. Other manufacturers of stents included in TA152 have indicated that there has been no change to their CE marked indications. The table below outlines some of the new stents which have come to market since the publication of TA152.

Details of new products

Stent (manufacturer)	**Details (phase of development, expected launch date)**
Combo – bio-engineered, sirolimus eluting (OrbusNeich)	CE marked
Biomime – sirolimus eluting (Meril Life Sciences)	CE marked
Resolute Integrity; Endeavor Resolute – both zotarolimus eluting (Medtronic)	CE marked
Xience Pro – everolimus eluting (Abbott Vascular) Xience PROx – everolimus eluting (Abbott Vascular) Xience Pro 48 – everolimus eluting (Abbott Vascular)	CE marked
Promus range – everolimus-eluting stents (Boston Scientific) Taxus Element – paclitaxel-eluting (Boston Scientific) Synergy – everolimus eluting (Boston Scientific)	CE marked
Biomatrix ; BioMatrix Flex; Axxess bifurcation stent – all biolimus A9 eluting (Biosensors)	CE marked
Coracto – sirolimus eluting stent system (Alvi Medica)	CE marked
Nobori - biolimus A9 eluting (Terumo)	CE marked
Monarch - paclitaxel eluting (Insitu Technologies)	CE marked
Infinnium - paclitaxel eluting (Sahajanand)	CE marked

Stent (manufacturer)	Details (phase of development, expected launch date)
Coroflex Please - paclitaxel eluting (B Braun)	CE marked
Vita - tretinoin-eluting stent (Aachen resonance)	CE marked
Cre8 – sirolimus eluting (CID SpA)	CE marked
DESyne - novolimus eluting (Elixir Medical)	CE marked
TaxCor – paclitexel eluting (Eurocor)	CE marked
Amazonia Pax; Nile Pax – paclitaxel eluting (Minvasys)	CE marked
Abrax – sirolimus eluting (Rontis) Phoenix – paclitaxel eluting (Rontis)	CE mark pending CE marked
Stentys (Stentys)	CE marked

Registered and unpublished trials

Trial name and registration number	Details
Comparison of the Biolimus A9-eluting Stent With the Zotarolimus - Eluting Stent in Multi-vessel PCI NCT01947439; BATTLE IN MULTI.	n=840 Estimated completion date: December 2017
A Prospective, Randomized Trial of BVS Veruss [sic] EES in Patients Undergoing Coronary Stenting for Myocardial Infarction NCT01942070; Ge IDE No. I0121.	Bioresorbable vascular scaffold vs. everolimus eluting stent n= 260 Estimated completion date: March 2015
Everolimus Stent in Myocardial Infarction NCT01684982; RACES-MI	Everolimus vs. sirolimus stent n=500 Completed

Trial name and registration number	Details
Comparison of the Angiographic Result of the Orsiro Hybrid Stent With Resolute Integrity Stent NCT01826552; NCT2356401; ORIENT.	n=375 Estimated primary completion date: September 2015 Estimated study completion date: December 2015
Early Effects of Intensive Lipid Lowering Treatment With Ezetimibe/ Simvastatin (Vytorin®) Assessed by Virtual Histology-Intravascular Ultrasound (VH-IVUS) and Optical Coherence Tomography (OCT) on Plaque Characteristics in Patients With Acute Coronary Syndrome NCT01857843; 1-2009-0032.	2x2 design. Subjects randomised to zotarolimus or sirolimus stenting + one of two add-on lipid-lowering therapies. n=160 Estimated primary completion date: November 2013 Estimated study completion date: December 2013
Reservoir-Based Polymer-Free Amphilimus-Eluting Stent Versus Polymer-Based Everolimus-Eluting Stent in Diabetic Patients NCT01710748; SEC-RES-2012-01; RESERVOIR	n=112 Estimated primary completion date: July 2014 Estimated study completion date: October 2014
Treatment of Coronary In-Stent Restenosis NCT01735825; FNO-KVO 631/2011 Pleva.	Paclitaxel coated balloon catheter vs. everolimus eluting stent. n=120 Estimated primary completion date: January 2015 Estimated study completion date: June 2015
Comparison of BIOdegradable Polymer and DuRablE Polymer Drug-eluting Stents in an All COmeRs PopulaTion (BIO-RESORT) NCT01674803; BIO-RESORT.	Sirolimus vs. everolimus vs. zotarolimus eluting stents. n= 3540 Estimated completion date: November 2016

Trial name and registration number	Details
A Safety and Efficacy Study of Paclitaxel-eluting Balloon to Paclitaxel-eluting Stent NCT01622075; AE-V-S-1001; PEPCAD	n=220 Completed
DESTINY TRIAL (Inspiron x Biomatrix) NCT01856088; Scitech004.	Sirolimus vs. biolimus eluting stents n= 165 Estimated primary completion date: November 2013 Estimated study completion date: February 2018
Serial EValuation of multiplE Coronary Artery Diseases by an Optical Coherence Tomography; Assessment of the Changes of de Novo Lesions and Comparisons of Neointimal Coverage Between Xience Prime® Versus Cypher SelectTM Stents; SEVEN-Xience Study NCT01856374; 1-2010-0052.	n=60 Estimated primary completion date: January 2014 Estimated study completion date: April 2014
Randomized Trial of Coronary Angioplasty for de Novo Lesions in sMall vesSElS With Drug Eluting Balloon. NCT01722799; MEIX-STENT-001, RAMSES-DEB.	Paclitaxel eluting balloon vs. zotarolimus eluting stent n=290 Estimated primary completion date: January 2014 Estimated study completion date: January 2015
Intravascular ULTrasound Guided Versus Conventional Angiography Guided Strategy to Deploy Zotarolimus and Everolimus Eluting Third Generation Stents in the Long Coronary Artery Lesions: ULTRA-ZET Trial NCT01979744; 1-2013-0052.	n=1116 Estimated primary completion date: October 2016 Estimated study completion date: October 2017

Trial name and registration number	Details
Evaluation of Neointimal Coverage of EES and BMS After Implantation in STEMI Patients by Optical Coherence Tomography NCT01875835; HMUOCT-STEMI; NEOCOVER.	n=60 Estimated primary completion date: April 2014 Estimated study completion date: December 2014
TRANSFORM OCT TRiple Assessment of Neointima Stent FOrmation to Reabsorbable polyMer With Optical Coherence Tomography NCT01972022; TRANSFORM; 1207/2013.	Everolimus vs. zotarolimus eluting stents. n=90 Estimated primary completion date: March 2016 Estimated study completion date: September 2016
Intracoronary Stenting and Angiographic Results: ORSIRO Stents Versus Xience PRIME Stents Assessed by Optical Coherence Tomography NCT01594736; MJ-MRI-ORSIRO_OCT-V3.1.	n=30 Estimated primary completion date: September 2013 Estimated study completion date: January 2015
ABSORB STEMI: the TROFI II Study NCT01986803; ECRI-003.	Trial of two types of everolimus eluting stents. n=190 Estimated primary completion date: March 2015 Estimated study completion date: September 2017.

Trial name and registration number	Details
A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-segment Elevation Myocardial Infarction EXAMINATION; EXAM-08.	Everolimus-eluting vs. non-DES n = 1500 Estimated completion date: January 2015 Results up to one year have been presented.
Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent NCT01233453; NL25754.101.08; COMPARE-II	n = 2700 Estimated completion date: December 2015.
The COOPerative Establishment for Necessary Investigation in Clinical Outcome After Stenting NCT01534221; COPERNICOS	Single centre study on various DESs and BMSs (exact brands TBC), with both randomised and non-randomised intervention arms. n = 5100 Estimated completion date: March 2021
Test Safety and Efficacy of Second Generation Zotarolimus- and Everolimus-Eluting Stents (ZES/EES) Assessed by Optical Coherence Tomography NCT01230723; GE IDE No. S03210; ZES/EES-OCT.	n = 30 Estimated completion date: July 2012
Test Safety of Biodegradable and Permanent Limus-Eluting Stents Assessed by Optical Coherence Tomography NCT01097434; GE IDE No. S03110; TEST-6-OCT.	Completed n = 48
Sirolimus-eluting Stents With Biodegradable Polymer Versus an Everolimus-eluting Stents NCT01443104; 065/11.	n = 2100 Estimated primary completion date: June 2014 Estimated completion date: May 2018

Trial name and registration number	Details
Firebird 2 Versus Excel Sirolimus-eluting Stent in Treating Real-world Patients With Coronary Artery Disease NCT01373632; 20110611; FESTA.	n = 570 Estimated completion date: September 2013
Impact of Intravascular Ultrasound(IVUS)-Guided Chronic Total Occlusion Intervention With Drug-eluting Stents NCT01563952; 1-2010-0023; CTO.	4 arms – biolimus or everolimus eluting stents ± ultrasound guiding n = 400 Estimated completion date: October 2013
BioFreedom FIM Clinical Trial NCT01172119; 08EU01.	Biolimus vs paclitaxel eluting stents n = 182 Primary completion date: June 2010 Estimated completion date: July 2014
Neointimal Coverage After Implantation of Biolimus Eluting Stent With Biodegradable Polymer: Optical Coherence Tomographic Assessment According to the Treatment of Dyslipidemia and Hypertension and the Types of Implanted Drug-eluting Stents NCT01502904; 1-2010-0007.	Sirolimus vs. biolimus eluting stents n = 120 Estimated completion date: July 2012.
Outcome of Second Generation Drug-eLuting Stents in Patients With Diabetes Mellitus NCT01293773; 007/CE-RMB; OCELOT.	n = 750 Estimated completion date: December 2012 Current status unknown.
Intra-Individual Comparison of Sirolimus and Paclitaxel Coated Stent (FRE-RACE Study) NCT00130546; FreRace-Study 186/02.	Completed n = 112

Trial name and registration number	Details
Everolimus-eluting (PROMUS-ELEMENT) vs. Biolimus A9-Eluting (NOBORI) Stents for Long-Coronary Lesions NCT01186120; 2010-0036; LONG-DES V.	n = 500 Completed.
Comparison of Zotarolimus-Eluting Stent vs Sirolimus-Eluting Stent for Diabetic Patients NCT01186107; 2009-0220; ESSENCE-DM2.	n = 260 Estimated completion date: March 2013
Effects of DES Platforms on Markers of Endothelial Damage and Inflammation NCT01489202; 655/2011/D; PLATFORM.	Platinum vs cobalt DESs n = 100 Estimated completion date: December 2016
Comparison of Cilotax Stent and Everolimus -Eluting Stent With Diabetes Mellitus (ESSENCE-DM III) NCT01515228; CVRF2011-11.	n = 300 Estimated completion date: January 2014
Optical Coherence Tomography Comparison of Neointimal Coverage Between CRE8 DES and BMS NCT01543373; C21101; DEMONSTRATE.	n = 40 Estimated completion date: June 2013
Safety and Efficacy Study Comparing 3 New Types of Coronary Stents NCT01166685; BASKET-PROVE II; BPII.	Biolimus A9 eluting vs. everolimus eluting vs. bare-metal stents. n = 2400 Estimated primary completion date: April 2012 Estimated completion date: May 2014
LONG-DES VI (Drug Eluting Stent for Long Lesions in Coronary Artery) NCT01489761; CVRF2011-9.	Zotarolimus vs. everolimus eluting stents. n = 400 Estimated completion date: February 2014

Trial name and registration number	Details
XIENCE V Everolimus Eluting Coronary Stent System (EECSS) China: Post-Approval Randomized Control Trial (RCT) NCT01178268; 10-387.	n = 546 Estimated completion date: February 2014
Hybrid Sirolimus-eluting Versus Everolimus-eluting Stents for Total Coronary Occlusions NCT01516723; RDC-2011-02; PRISON-IV.	n = 330 Estimated completion date: May 2018.
A New Strategy Regarding Discontinuation of Dual Antiplatelet NCT01145079; 4-2009-0115.	Zotarolimus, sirolimus and everolimus eluting stents. n = 2120 Completed.
International Randomized Comparison Between DES Limus Carbostent and Taxus Drug Eluting Stents in the Treatment of De-novo Coronary Lesions NCT01373502; C20902; NEXT.	n = 323 Estimated completion date: September 2015
NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-eluting Stent Trial NCT01303640; C494.	n = 3200 Estimated completion date: August 2015
Efficacy of Everolimus-Eluting Versus Zotarolimus-Eluting Sten [sic] for Coronary Lesions in Acute Myocardial Infarction NCT01347554; EVZT_1.0; EVERZOTA.	n = 500 Estimated primary completion date: December 2011 Estimated completion date: December 2012
Comparison of Biolimus-eluting Biodegradable Polymer, Everolimus-eluting and Sirolimus-eluting Coronary Stents NCT01268371; BESS	n = 3000 Estimated completion date: December 2013

Trial name and registration number	Details
ComparisiOn of Neointimal coVerage betwEen ZES and EES Using OCT at 3 Months NCT01091740; 1-2009-0010; COVER OCT-II.	n = 40 Completed
China Made Sirolimus Eluting Stent for Intermediate Lesion NCT01375296; RJH20100918; SESIL.	Status unknown Sirolimus eluting stent vs. “routine medicine” n = 600 Primary completion date: October 2011 Estimated completion date: November 2011
COmplex BifuRcation Lesions: a Comparison Between the AXXESS Device and Culotte Stenting: an Optical Coherence Tomography (OCT) Study NCT01486095; UH Leuven S53441; COBRA.	n = 40 Primary completion date: December 2012 Estimated completion date: December 2013
Activity of Platelets After Inhibition and Cardiovascular Events Optical Coherence Tomography Study NCT01239654; APICE OCT Study (Project 4)	Everolimus vs. zotarolimus-eluting stents n = 17 Completed
Study of the Orsiro Drug Eluting Stent System NCT01356888; C1004; BIOFLOW-II.	Sirolimus eluting vs. everolimus eluting stents. n = 440 Primary completion date: July 2013 Estimated completion date: April 2017
Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DEsS Candidates (ZEUS) Study NCT01385319; ZEUS-10-II.	Vs. bare-metal stent n = 1600 Primary completion date: December 2012 Estimated completion date: April 2017

Trial name and registration number	Details
Comparison of the DES With Bio-degradable Polymer and Durable Polymer NCT01397175; CHOICE.	n = 2880 Primary completion date: July 2014 Estimated completion date: July 2015

References

Alazzoni A, Al-Saleh A, Jolly SS (2012) Everolimus-Eluting versus Paclitaxel-Eluting Stents in Percutaneous Coronary Intervention: Meta-Analysis of Randomized Trials. *Thrombosis.* 2012: 126369-.

Amin AP, Reynolds MR, Lei Y et al. (Sept. 2012) Cost-effectiveness of everolimus- versus paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization (from the SPIRIT-IV Trial). *American Journal of Cardiology.* 110 (6): 765-770.

Ba B, Ma YT, Yu ZX et al. (2012) Optimal duration of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: a meta-analysis (Provisional abstract). *Database of Abstracts of Reviews of Effects.* (4): 577-582.

Bangalore S, Amoroso N, Fusaro M et al. (Aug. 2013a) Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. *Circulation: Cardiovascular Interventions.* 6 (4): 378-390.

Bangalore S, Toklu B, Amoroso N et al. (2013b) Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ.* 347: f6625-.

Baumler M, Stargardt T, Schreyogg J et al. (2012) Cost effectiveness of drug-eluting stents in acute myocardial infarction patients in Germany: results from administrative data using a propensity score-matching approach (Structured abstract). *Applied Health Economics and Health Policy.* 10 (4): 235-248.

Cassese S, Desch S, Kastrati A et al. (June 2013) Polymer-free Sirolimus-eluting Versus Polymer-based Paclitaxel-eluting Stents: An Individual Patient Data Analysis of Randomized Trials. *Revista Espanola de Cardiologia.* 66 (6): 435-442.

Crawford-Faucher A (2012) Prolonged clopidogrel use after cardiac stenting is not beneficial. *American Family Physician.* 86 (9): 853-.

De la Torre Hernandez JM, Alfonso F, Sanchez RA et al. (Mar. 2013) Comparison of paclitaxel-eluting stents (Taxus) and everolimus-eluting stents (Xience) in left main coronary artery disease with 3 years follow-up (from the ESTROFA-LM registry). *American Journal of Cardiology.* 111 (5): 676-683.

Ellis SG, Stone GW, Cox DA et al. (Dec. 2009) Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). *Jacc: Cardiovascular Interventions.* 2 (12): 1248-1259.

Fan J, Du H, Yin Y et al. (Sept. 2013) Efficacy and safety of zotarolimus-eluting stents compared with sirolimus-eluting stents in patients undergoing percutaneous coronary interventions--a meta-analysis of randomized controlled trials. *International Journal of Cardiology.* 167 (5): 2126-2133.

Frohlich GM, Lansky AJ, Ko DT et al. (2013) Drug eluting balloons for de novo coronary lesions - a systematic review and meta-analysis. *BMC Med.* 11: 123-.

Geng DF, Meng Z, Yan HY et al. (June 2013) Bare-metal stent versus drug-eluting stent in large coronary arteries: meta-analysis of randomized controlled trials. *Catheterization & Cardiovascular Interventions.* 81 (7): 1087-1094.

Gray WA, Yeung AC, Cutlip DE et al. (May 2012) A randomized, controlled, multi-center trial comparing the safety and efficacy of zotarolimus-eluting and paclitaxel-eluting stents in de novo lesions in coronary arteries: final results of the ZoMaxx II trial. *International Journal of Cardiology.* 157 (1): 96-101.

Gwon HC, Hahn JY, Park KW et al. (2012) Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation.* 125 (3): 505-513.

Hansen KW, Kaiser C, Hvelplund A et al. (Oct. 2013) Improved two-year outcomes after drug-eluting versus bare-metal stent implantation in women and men with large coronary arteries: Importance of vessel size. *International Journal of Cardiology.* 169 (1): 29-34.

Holmvang L, Kelbaek H, Kaltoft A et al. (June 2013) Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 5 years follow-up from the randomized DEDICATION trial (Drug Elution and Distal Protection in Acute Myocardial Infarction). *Jacc: Cardiovascular Interventions.* 6 (6): 548-553.

Jensen LO, Thayssen P, Christiansen EH et al. (Sept. 2012) 2-year patient-related versus stent-related outcomes: the SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome IV) Trial. *Journal of the American College of Cardiology.* 60 (13): 1140-1147.

Liistro F, Porto I, Angioli P et al. (Nov. 2013) Elutax paclitaxel-eluting balloon followed by bare-metal stent compared with Xience V drug-eluting stent in the treatment of de novo coronary stenosis: A randomized trial. *American Heart Journal.* 166 (5): 920-926.

Luca G, Dirksen MT, Spaulding C et al. (2012) Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials (Structured abstract). *Archives of Internal Medicine.* 172 (8): 611-621.

Lupi A, Rognoni A, Secco GG et al. (2013) Drug eluting balloon versus drug eluting stent in percutaneous coronary interventions: insights from a meta-analysis of 1462 patients (Provisional abstract). *Database of Abstracts of Reviews of Effects.* (4): epub-.

Rodriguez AE, Rodriguez-Granillo AM, Antoniucci D et al. (Sept. 2012) Randomized comparison of cost-saving and effectiveness of oral rapamycin plus bare-metal stents with drug-eluting stents: three-year outcome from the randomized oral rapamycin in Argentina (ORAR) III trial. *Catheterization & Cardiovascular Interventions.* 80 (3): 385-394.

Sabate M, Cequier A, Iniguez A et al. (Oct. 2012) Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet.* 380 (9852): 1482-1490.

Serruys PW, Farooq V, Kalesan B et al. (Aug. 2013) Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *Jacc: Cardiovascular Interventions.* 6 (8): 777-789.

Smits PC, Hofma S, Togni M et al. (Feb. 2013) Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet.* 381 (9867): 651-660.

Tada T, Byrne RA, Cassese S et al. (Jan. 2013) Comparative efficacy of 2 zotarolimus-eluting stent generations: resolute versus endeavor stents in patients with coronary artery disease. *American Heart Journal.* 165 (1): 80-86.

Turco MA, Kansal AR, Stern S et al. (2012) Economic modeling of new stent platforms to evaluate cost effectiveness: analysis of the TAXUS Liberte versus TAXUS express stents (Provisional abstract). *Journal of Interventional Cardiology.* 25 (4): 353-363.

Wang L, Zang W, Xie D et al. (2013) Drug-eluting stents for acute coronary syndrome: a meta-analysis of randomized controlled trials. *PLoS ONE [Electronic Resource].* 8 (9): e72895-.

Willich SN, Muller-Riemenschneider F, McBride D et al. (2013) Health economic evaluation of the use of drug-eluting stents: first results from the Drug-Eluting Stent Registry (DES.de) (Provisional abstract). *Herz.* 38 (1): 57-64.

Wisloff T, Atar D, Sonbo K, I (Nov. 2013) Cost effectiveness of drug-eluting stents as compared with bare metal stents in patients with coronary artery disease. *American Journal of Therapeutics.* 20 (6): 596-601.

Appendix 3 – Implementation submission

1. Routine healthcare activity data

1.1. Hospital Episode Statistics data

This section presents hospital episode statistics (HES) online data for the number of percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery (OPCS procedure code K75.1) finished consultant episodes conducted in England, between 2006/07 and 2012/13 (figure 1).

Figure 1 Number of percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery finished consultant episodes conducted in England

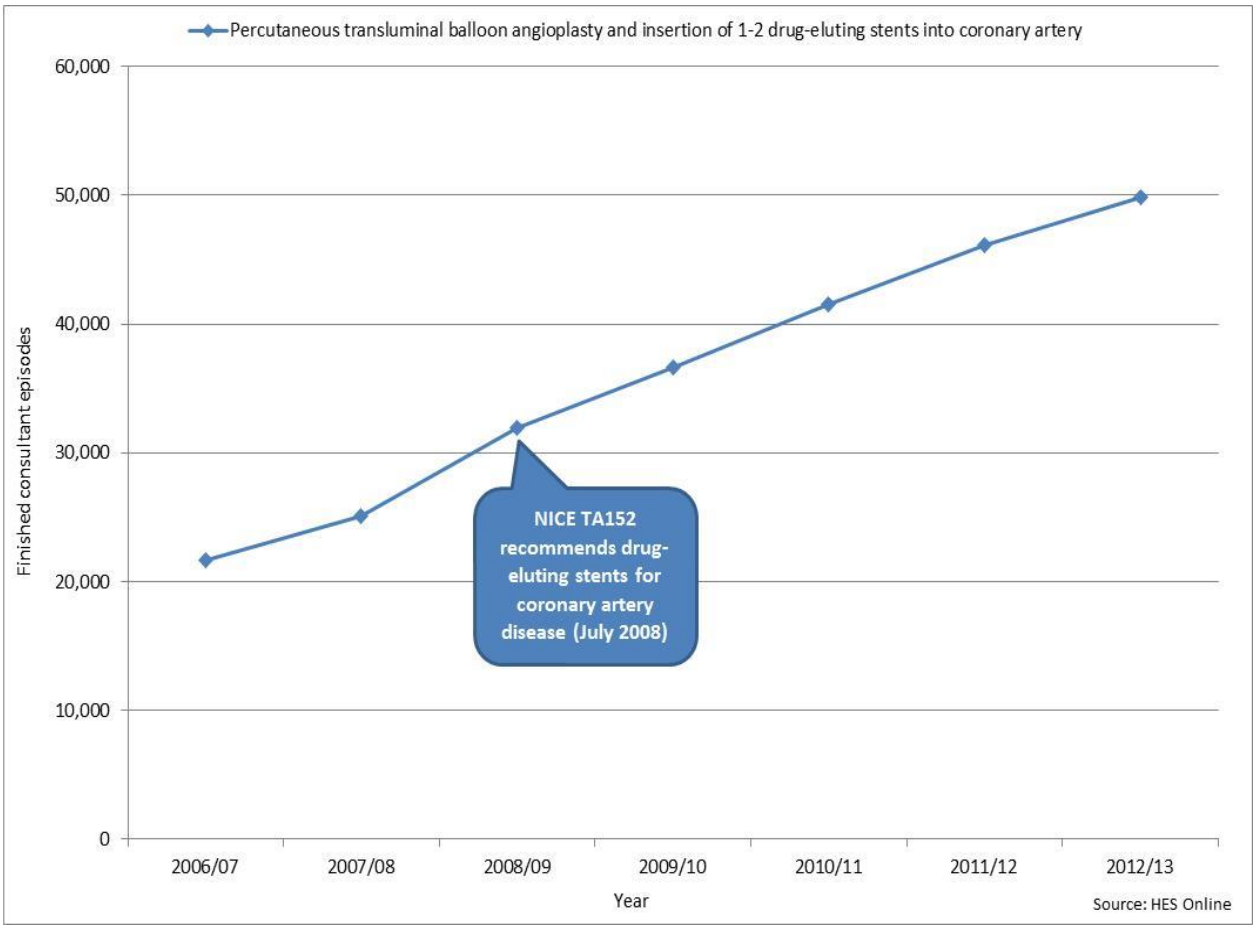
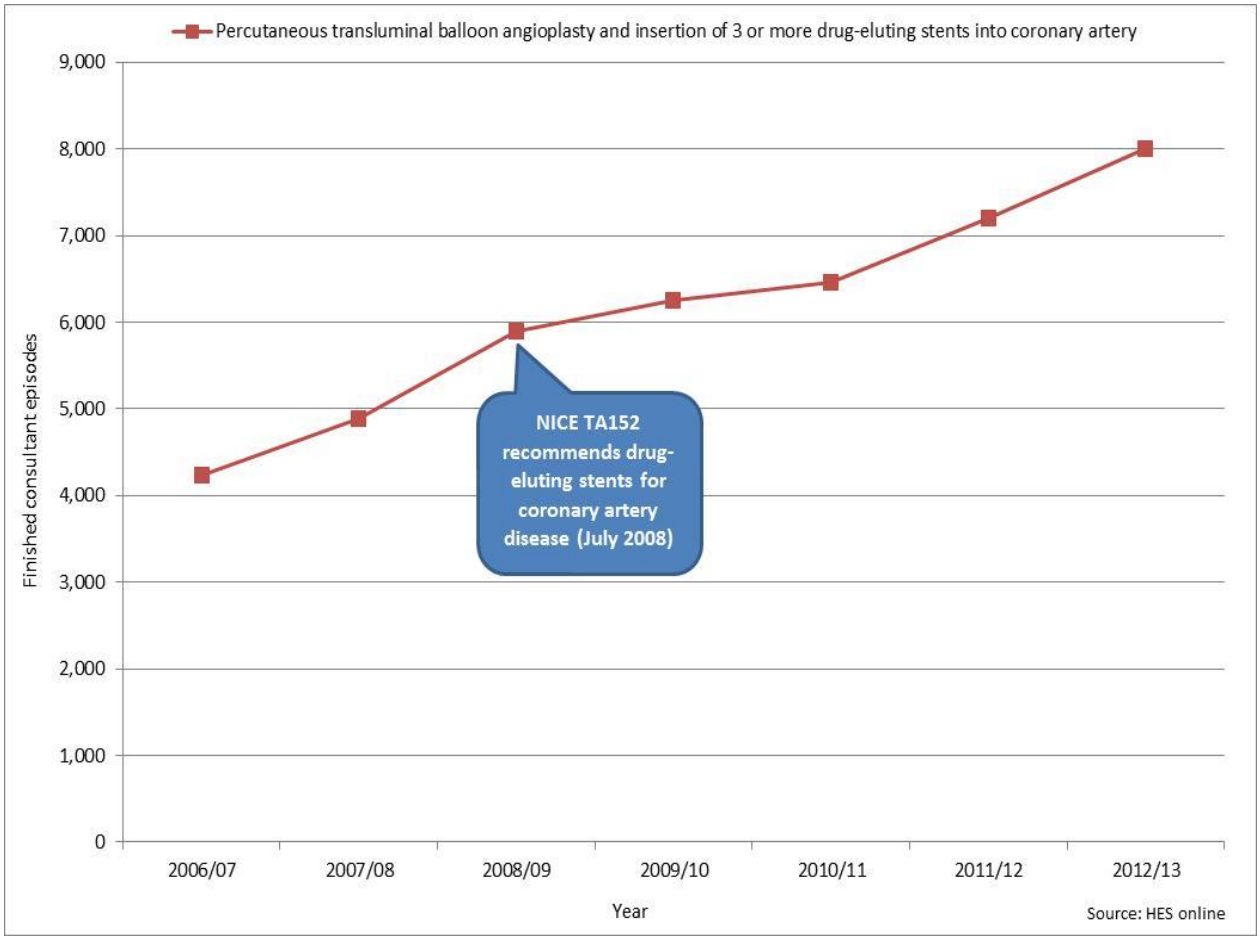


Figure 2 below presents hospital episode statistics (HES) online data for the number of percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery (OPCS procedure code K75.2) finished consultant episodes conducted in England, between 2006/07 and 2012/13.

Figure 2 Number of percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery finished consultant episodes conducted in England



2. Implementation studies from published literature

Information is taken from the uptake database website.

2.1 The NHS Information Centre for Health and Social Care (2009) Audit of Angioplasty Procedures 2009

A UK wide audit performed by the British Cardiovascular Intervention Society (BCIS). Following concerns about the safety of drug eluting stents in September 2006, there was a fall in their use to 55 per cent across the UK. Data from 2008 suggest a gradual increase in their use now that safety issues are better understood. Research suggests that compliance with the NICE guidance would result in about 70 to 80 per cent of patients being treated with a drug eluting stent.

2.2 NHS Information Centre for Health and Social Care/ British Cardiovascular Intervention Society (2011) National audit of angioplasty procedures 2010

This audit aims to improve the care of patients who undergo percutaneous coronary

intervention (PCI) procedures in the UK. Of 88 NHS PCI centres in the UK, all but 5 submitted data for procedures performed between 1st January and 31st December 2009. Results showed that overall use of stents remains high at 92%, with a gradual increase in the percentage of patients treated with drug eluting stents. In 2009 on average centres used drug eluting stents in 63.5% of cases.

2.3 National Institute for Cardiovascular Outcomes Research, University College London (2012) National Audit of Percutaneous Coronary Interventional Procedures: Annual Report 2011

This 2010 audit on Percutaneous Coronary Interventional Procedures (PCIs) included data submitted by 94 of 97 NHS PCI centres and 6 of 17 private hospitals in the UK. A total of 87,676 PCIs were performed, of which the results found that 92% involved stent insertion, as recommended by NICE for patients with angina or with acute myocardial infarction. It was noted that there has been a gradual increase in the percentage of patients treated with drug eluting stents.

2.4 Health and Social Care Information Centre (2013) NICE Technology Appraisals in the NHS in England 2011; Experimental Statistics - Innovation Scorecard

This experimental report presents data in the format of an interactive reporting spreadsheet, attempting to assess compliance with NICE TAs by NHS organisations. A total of 102 TAs are included, covering 76 medicines and 6 medical device technologies. For medicines, this Scorecard reports on the calendar year 2011 and considers medicines recommended before July 2011. The report describes data currently available and the limitations in using this data to assess compliance.

2.5 National Institute for Cardiovascular Outcomes Research, University College London (2013) National Audit of Percutaneous Coronary Interventional Procedures: Annual Public Report January 2011 - December 2011

This 2011 UK audit on Percutaneous Coronary Interventional Procedures (PCIs) included data from 97/99 NHS PCI centres and 7/18 private hospitals. A total of 88,692 PCIs were performed, of which 92% involved stent insertion. Following concerns about the safety of drug eluting stents in September 2006, there was a fall in use to 55% across the UK. Data from 2011 suggest an increase in use (71%) now that safety issues are better understood. However there are large differences in usage across the UK.

2.6 Health and Social Care Information Centre (2013) NICE Technology Appraisals in the NHS in England 2012; Experimental Statistics - Innovation Scorecard

This experimental report presents data in the format of an interactive reporting spreadsheet, attempting to assess compliance with NICE TAs by NHS organisations. A total of 121 TAs are included, covering 88 medicines and 6 medical device technologies. For medicines, this Scorecard reports on the calendar year 2012 and considers medicines recommended before July 2012. The report describes data currently available and the limitations in using this data to assess compliance.

2.7 MINAP (2013) Myocardial Ischaemia National Audit Project: How the NHS cares for patients with heart attack. Annual Public Report April 2012 - March 2013

This 12th annual MINAP Public Report presents analyses from all hospitals and ambulance services in England, Wales and Belfast, that provided care for patients with suspected heart attack in 2012/13. Results found the proportion of all MINAP heart attack patients that received primary percutaneous coronary intervention (PCI) was 72% in England, and in Wales was 55%. Use of secondary prevention medication at discharge continues to exceed the national standards at 95%.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

> *"One person commented that there had been difficulty with managing decision-making whilst awaiting the drug-eluting stents guidance; however this had been addressed since the guidance has been published. Another person suggested whether NICE could supply a cost calculator that showed the price needed for good value, enabling local organisations to adjust their policy accordingly".*

Appendix 3A: Healthcare activity data definitions

Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) are the national statistical data warehouse for England of the care provided by NHS hospitals and for NHS hospital patients treated elsewhere. HES are the data source for a wide range of healthcare analysis. It contains admitted patient care data from 1989 onwards.

The HES Interrogation System is an online version of the data. The NHS Information Centre maintains the system.

Finished Consultant Episode (FCE): The FCE is a period of admitted patient care under one consultant within one healthcare provider. The figures do not represent the number of patients, as a person may have more than one episode of care within the year.

Main operation: The main operation is the first recorded operation in the HES data set and is usually the most resource intensive procedure performed during the episode.

Secondary operation: As well as the main operative procedure, there are up to 19 secondary operation fields in Hospital Episode Statistics (HES) that show secondary or additional procedures performed on the patient during the episode of care.