

Addendum to report

The following pages include an addendum to clarify which studies were included by the sponsor, and to also provide textual description of those studies reported by the sponsors to be 'included'. Ten studies have been removed from table 1 that were described by the sponsor as 'relevant', but were subsequently described as 'excluded'. Details in table 1b for the reference 'Safi 2001' which should have read 'Safi 2007' have been amended. An erratum has been added for section 3.9. Further, the EAC has added a comment on a potentially relevant study that is now in press, and that the EAC received on 16 June 2013 from the sponsor, which was too late to be included in the body of the report.

Herewith we provide a revised section 3.3 and revised tables 1 and 1b.

KITEC EAC 27 June 2013

3.3 Included and excluded studies (section revised)

The sponsor initially reported finding 18 published studies of which 13/18 studies were reported as being 'relevant' (Jakob 2012, Jakob 2011, Hoffman 2012, Gorlitzer 2012, Pacini 2011, Tsagakis 2010a, Jakob 2010, Tsagakis 2011, Tsagakis 2010b, Di Bartolomeo 2009, Di Bartolomeo 2008, Gorlitzer 2007, Herold 2006). The sponsor subsequently excluded 10/13, leaving just three (Jakob 2012, Jakob 2011, and Hoffman 2012). Details of these three studies are given in table 1 and described below.

All three studies included by the sponsor are descriptive and none included comparators (table 1). Jakob et al (2011) reports on the International E-vita Open Registry and provides data from January 2005 to December 2010. This includes 274 patients with complex aortic disease who were enrolled into the registry. The majority were male (74%) and mean age was 60 years. At the time of publication of Jakob's study, the registry included eight referral centres in Europe: Barcelona, Birmingham, Bologna, Essen, Graz, Leipzig, Prague, and Vienna. The maximum follow-up was six years. This is the most comprehensive paper and includes the best quality evidence available (discussed below).

Jakob 2012 also reports on patients from the International E-vita Open Registry and included patients receiving surgery between January 2005 and March 2011, a three-month longer span than the Jakob 2011 paper. However, Jakob 2012 only included the 77 patients from the Essen (Germany) centre, and so the patients are a subset of the entire registry. Unsurprisingly, mean age and the proportion of males were similar to the whole registry reported in Jakob 2011 (mean 59 years, 75% males). The maximum follow-up was six years. Hoffman's 2012 study was small with just 32 patients treated in Aachen, Germany. Their mean age was 58 years and 81% were males. This was a single centre study but was not part of the International E-vita Open Registry. The study included patients with acute Stanford type A aortic dissection who underwent the frozen elephant trunk procedure (E-vita open

plus) for replacement of the aortic arch and stenting of the descending aorta, between November 2009 and September 2011. The maximum follow-up was 33 months.

The sponsor reported (in reference to Jakob 2011) that they:

'decided to focus on the results published in this article. We excluded from our analysis articles published before as:'

This was followed by the list of the 10/13 studies to be excluded. The reason for exclusion was not totally clear but the EAC considers that for the papers that reported on subsets of the International E-vita Open Registry, their exclusion is appropriate as their data largely overlap with the data provided in the Jakob 2011 paper. Studies that this applies to are as follows: Pacini 2011, Tsagakis 2010a, Jakob 2010, Tsagakis 2011. For the other papers excluded, the EAC also considers this appropriate. Specifically Gorlitzer 2012 included just three patients from Vienna who received emergent E-vita open and so these data are appropriately excluded. Tsagakis 2010b is a two-part study in Essen: i) an animal study, and ii) the clinical use of E-vita open plus in nine (human) patients. This study provided limited outcomes in humans and no follow-up and so the EAC considers its data to be unusable here. Di Bartolomeo 2009 included 34 patients from Bologna, between January 2007 and July 2008. Bologna is one of the International E-vita Open Registry centres but it was not clear if this series of patients were included in the registry. Follow-up was short at 12 months maximum and a mean of 9 months. Given the doubt about overlap and the limited data, the EAC considers these data to be appropriately excluded. Di Bartolomeo 2008 reports on 24 patients receiving surgery between January 2007 and January 2008 from the same centre and it seems likely that these are a subset of the 34 patients described above. Hence the EAC considers that these data are appropriately excluded. Gorlitzer 2007 included seven patients receiving surgery in Vienna. This was also one of the International E-vita Open Registry centres and so the data may be included in the Jakob 2011 study report. The EAC concludes that this, together with its small size and short follow-up,

preclude its inclusion. Finally, Herold 2006 reports on a study in 30 patients from Essen, a registry centre and so as with other papers above, seems likely to overlap with the Jakob 2011 series. Hence the EAC agrees that this must be excluded.

One additional paper reported by the sponsor as unobtainable in its complete form: 'Management of postdissection thoracoabdominal aneurysm after previous frozen classical ET with the E-vita Open Plus stent-graft' was also excluded by the sponsor. The EAC was similarly unable to find this paper. However, the EAC did identify a different study published as a conference abstract by Mestres (2012) that was not cited by the sponsor. This study described a series of patients treated in Barcelona, one of the registry centres. The EAC received a pre-publication copy of this paper on 16 June 2013 and it is clear that this is a subset of the International E-vita Open Registry data and so the EAC considers it not appropriate for inclusion.

The sponsor chose to use only the data from Jakob 2011 and not to use data from Jakob 2012 or Hoffman 2012 in its evidence for E-vita open. The EAC considers that this is reasonable because Jakob 2012 overlaps considerably with Jakob 2011 and Hoffman's study was small, with 32 patients, and had a short follow-up.

However while the Jakob (2011) study provides a full and thorough account of the use of the device, it was confusing that the sponsor described Jakob 2012 and Hoffman 2012 as 'relevant' and did not explicitly say that they were excluding them.

The four comparator studies (table 1b) only described outcomes in patients who had undergone two-stage open surgical repair with vascular graft replacement. These studies were observational, and all were from the USA (New York, Cleveland Ohio, Houston Texas) while the E-vita open evidence was all from Europe. The comparator studies were all conducted between

1990 and 2006, therefore most of the evidence preceded the E-vita open plus registry. As described above and reported in detail below, the EAC conducted a systematic review on comparators and have conducted a thorough meta-analysis of outcomes.

Table 1: Summary of key points from sponsor-included E-Vita open plus studies

Reference	Study used by sponsor in evidence synthesis?	Study	Patient population	Inter-vention	Country	Age/Sex	Study design	Sample size	Comments
Jakob et al., 2011	YES	The International E-vita Open Registry	Jan 2005 to Dec 2010. Patients with complex aortic disease underwent arch replacement combined with open antegrade stent-grafting using the E-vita open hybrid stent-graft and have enrolled to the international E-vita Open Registry (IEOR).	E-vita open	International E-vita Open Registry (IEOR). 8 referral centres: Barcelona (Spain), Birmingham (UK), Bologna (Italy), Essen (Germany), Graz (Austria), Leipzig (Germany), Prague (Czech Republic), Vienna (Austria)	Mean age= 60; 74% males	Multi-centre cohort study with up to 6 years follow-up	n=274 (AAD=88, CAD=102, TAA=84)	<ul style="list-style-type: none"> • Multi-centre study using register data • No CIs for estimates • No comparator in paper • Numbers in some subgroups are very small • Any centre effect? • Large data set with data collected in uniform manner

Reference	Study used by sponsor in evidence synthesis?	Study	Patient population	Inter-vention	Country	Age/Sex	Study design	Sample size	Comments
Jakob et al., 2012	NO	Six-year experience with a hybrid stent graft prosthesis for extensive thoracic aortic disease: an interim balance.	Jan 2005 to Mar 2011. Patients with complex thoracic aortic disease underwent arch replacement combined with antegrade stent grafting of the descending aorta using the E-vita open hybrid stent graft in West German Heart Centre, University of Duisburg-Essen, Essen, Germany.	E-vita open	Essen, Germany	Mean age= 59; 75% males	Cohort study with up to 66 months follow-up	n=77 (AAD=39, CAD=23, TAA=15)	<ul style="list-style-type: none"> • Subset of the International E-vita Open Registry • Single-centre study • No CIs for estimates • No comparator
Hoffman et al., 2012	NO	Thoracic stent graft sizing for frozen elephant trunk repair in acute type A dissection.	Nov 2009 to Sep 2011. Patients with acute Stanford type A aortic dissection underwent the frozen elephant trunk procedure (E-vita open plus) for replacement of the aortic arch and stenting of the descending aorta, at University Hospital RWTH Aachen, Aachen, Germany.	E-vita open plus	Aachen, Germany	Mean age= 58; 81% males	Cohort study with up to 33 months follow-up	n=32	<ul style="list-style-type: none"> • Single-centre study • Short follow-up • Descriptive statistics only • No comparator

AAD: Acute aortic dissection, CAD: Chronic aortic dissection, TAA: Thoracic aortic aneurysm, AD: aortic dissection, EAA: Extended aortic aneurysm, SD: Standard deviation, CI: Confidence interval, CPB: Cardiopulmonary bypass, SACP: Selective antegrade cerebral perfusion, HCA: Hypothermic circulatory arrest.

Table 1b Summary of key points from sponsor-reported comparator studies

Reference	Study	Patient population	Intervention	Country	Age/Sex	Study design	Sample size
Etz et al 2008	Staged repair of thoracic and thoraco-abdominal aortic aneurisms	February 1990 to September 2006. Consecutive patients who underwent total arch replacement.	Two-stage open surgical repair with vascular graft replacement	New York, USA	Median 68 years Range: 20 to 87 59% male	Observational study	215
Svensson et al 2004	Elephant trunk procedure: newer indications and uses	November 1990 to February 2003 . Consecutive patients who underwent total arch replacement.	Two-stage open surgical repair with vascular graft replacement	Cleveland, Ohio, USA	Mean 67 years (SD 10.5) 47% male	Retrospective observational	94
Safi et al 2007	Optimisation of Aortic Arch Replacement: Two-Stage approach	February 1991 to December 2005. Patients who underwent repair for extensive aortic aneurysm.	Two-stage open surgical repair with vascular graft replacement	Houston, Texas, USA	Mean 68 years Range: 16 to 87 51% male	Observational study	254
LeMaire et al 2006	The elephant trunk technique for staged repair of complex aneurysms of the entire thoracic aorta	1990 to 2005. Consecutive patients with extensive aneurysms.	Two-stage open surgical repair with vascular graft replacement	Houston, Texas, USA	Mean 66 years (SD10.3) 48% male	Observational study	205

Erratum: section 3.0, page 27.

‘The review of comparators found 1929 abstracts, which were screened and finally resulted in ten relevant studies (Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004, Kim et al 2009, Kawaharada et al 2009, Lee et al 2011, Antoniou et al 2010a, Antoniou et al 2010b), which also included five studies cited by the sponsor (Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004)’.

This should read:

‘The review of comparators found 1929 abstracts, which were screened and finally resulted in ten relevant studies (Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004, Safi et al 2004, Kim et al 2009, Kawaharada et al 2009, Lee et al 2011, Antoniou et al 2010a, Antoniou et al 2010b), which also included four studies cited by the sponsor (Etz et al 2008, Safi et al 2007, LeMaire et al 2006, Svensson et al 2004).