ΔΙΑΚΡΑΤΙΚΟ ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:

«Ενδαγγειακές Τεχνικές»

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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ: “HYBRID PROCEDURES; DO THEY HAVE A ROLE IN AORTIC ARCH PATHOLOGIES?”

ΜΕΤΑΠΤ. ΦΟΙΤΗΤΗΣ:

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ΑΘΗΝΑ

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<u>ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ</u>
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Του Μεταπτυχιακού Φοιτητή Νικολάου Παπακωνσταντίνου

<u>Εξεταστική Επιτροπή</u>

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Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της 13ης Ιανουαρίου 2010 για την αξιολόγηση και εξέταση του υποψηφίου κου **Νικολάου Παπακωνσταντίνου** του Αγγέλου, συνεδρίασε σήμερα _/_/2017

Η Επιτροπή διαπίστωσε ότι η Διπλωματική Εργασία τ. Κου **Νικολάου Παπακωνσταντίνου** με τίτλο **"Hybrid Procedures; Do They Have a Role In Aortic Arch Pathologies?"**, είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπ' όψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους .... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's).

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ...., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ...., και για τον βαθμό «ΚΑΛΩΣ» ψήφους .... Κατά συνέπεια, απονέμεται ο βαθμός «......................».

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ABSTRACT

Introduction

The treatment of choice for surgical therapy of aortic arch pathologies is conventional, open total arch replacement. However, the conventional open surgical repair is an invasive procedure, requiring cardiopulmonary bypass and deep hypothermic circulatory arrest leading to significant morbidity and mortality rates. A hybrid approach is a combination of tools available only in the catheterization laboratory with those available only in the operating room in order to gain maximum profit from both of them. The hybrid arch repair seeks to limit operative, bypass, and circulatory arrest times by making the arch repair procedure simpler and shorter. These “hybrid techniques” include aortic arch debranching without (type I) or with (type II) ascending aorta replacement and frozen elephant trunk procedure (type III) in case of extensive aortic disease.

Materials and methods

A detailed review of the literature, published from January 2013 until December 2016, concerning hybrid aortic arch reconstruction procedures was made and data for indications, morbidity and mortality associated with these procedures were extracted. The base of this study was Moulakakis’s et al meta-analysis who analyzed hybrid aortic arch reconstruction studies up to December 2012.

Results

As far as type I hybrid aortic arch reconstruction is concerned, among 122 patients included, the pooled endoleak rate was 10.78% (95%CI=1.94-23.40), 30-day or in-hospital mortality was 3.89% (95%CI=0.324-9.78), stroke rate was 3.79% (95%CI=0.25-9.77) and weighted permanent paraplegia rate was 2.4%, even better to Moulakakis et al meta-analysis, examining 956 patients, who reported 16.6% endoleak rate, 11.9% 30-day mortality rate, 7.6% stroke rate and 3.6% spinal cord ischemia rate. In terms of type II hybrid approach, among 40 patients, endoleak rate was 12.5%, 30-day or in-hospital mortality rate was 5.3%, stroke rate was 2.5%, no permanent paraplegia was noticed and late mortality rate was 12.5%. Finally, 989 patients were submitted to frozen elephant trunk procedure. Thirty-day or in-hospital pooled mortality rate (5.04% [95CI=1.13-10.74]) was lower to Moulakakis’s study

including 1316 patients (9.5%). An even lower than in Moulakakis's study pooled rate of stroke was reported (2.38% [95CI=0.13-6.30] vs 6.2%), as well as a lower pooled rate of irreversible paraplegia due to spinal cord injury (0.63% [95CI=0.00-2.73] vs 5%).

Conclusions

Hybrid aortic arch repair procedures extend the envelope of intervention in aortic arch pathologies, particularly in high-risk patients who are suboptimal candidates for open surgery. They are a safe alternative to open repair with acceptable short- and mid-term results. However, stroke and mortality rates remain noteworthy. Future prospective trials directly comparing open conventional techniques with hybrid or total endovascular approaches are required. Larger cohorts with longer follow-up should also be planned before applying hybrid procedures to low-risk patients, too.

Keywords: hybrid procedures; aortic arch; debranching; frozen elephant trunk

ΠΕΡΙΛΗΨΗ

Εισαγωγή

Η θεραπεία εκλογής στη χειρουργική αντιμετώπιση των παθήσεων του αορτικού τόξου είναι η συμβατική, ανοιχτή πλήρης αντικατάσταση του τόξου. Ωστόσο, η συμβατική, ανοιχτή χειρουργική αποκατάσταση είναι μια επεμβατική διαδικασία, η οποία απαιτεί εξωσωματική κυκλοφορία και παύση της καρδιακής λειτουργίας σε βαθιά υποθερμία που οδηγούν σε σημαντικά ποσοστά νοσηρότητας και θνητότητας. Η υβριδική προσέγγιση αφορά σε ένα συνδυασμό των μέσων που είναι διαθέσιμα μόνο στην αγγειογραφική σουίτα με εκείνα που είναι διαθέσιμα μόνο στη χειρουργική αίθουσα ώστε να αποκομιστεί το μέγιστο όφελος και από τις δύο προσεγγίσεις. Η υβριδική αποκατάσταση του τόξου αποσκοπεί στον περιορισμό του χειρουργικού χρόνου, του χρόνου της εξωσωματικής κυκλοφορίας και του χρόνου της παύσης της καρδιακής λειτουργίας, βραχύνοντας και απλοποιώντας τη διαδικασία της αποκατάστασης του αορτικού τόξου. Αυτές οι «υβριδικές τεχνικές» περιλαμβάνουν την αποκλαδοποίηση του αορτικού τόξου χωρίς (τύπος I) ή με (τύπος II) συνοδό αντικατάσταση της ανιούσας αορτής και την τεχνική της παγωμένης προβοσκίδας ελέφαντα («frozen elephant trunk», τύπος III) σε περίπτωση εκτεταμένης αορτικής νόσου.

Υλικά και μέθοδος

Πραγματοποιήθηκε μια ενδελεχής ανασκόπηση της βιβλιογραφίας, που έχει δημοσιευτεί από τον Ιανουάριο του 2013 μέχρι το Δεκέμβριο του 2016, η οποία αφορά στην υβριδική αποκατάσταση του αορτικού τόξου και εξάχθηκαν δεδομένα για τις ενδείξεις, τη νοσηρότητα και τη θνητότητα που συνδέεται με αυτές τις διαδικασίες. Η μετα-ανάλυση των Μουλακάκη και συνεργατών που ανέλυσε τις μελέτες για την υβριδική αποκατάσταση του αορτικού τόξου έως το Δεκέμβριο του 2012 αποτέλεσε τη βάση αυτής της μελέτης.

Αποτελέσματα

Όσον αφορά την τύπου I υβριδική αποκατάσταση του αορτικού τόξου, μεταξύ των 122 ασθενών που συμπεριελήφθησαν, το σταθμισμένο ποσοστό ενδοδιαφυγών ήταν 10.78% (95%CI=1.94-23.40), η θνητότητα 30 ημερών ή ενδονοσοκομειακή θνητότητα ήταν 3.89% (95%CI=0.324-9.78), το ποσοστό εγκεφαλικών ήταν 3.79%

(95%CI=0.25-9.77) και το ποσοστό μόνιμης παραπληγίας 2,4%, παρόμοια με τη μετα-ανάλυση των Μουλακάκη και συνεργατών, που εξέτασε 956 ασθενείς, στην οποία σημειώθηκε 16,6% ποσοστό ενδοδιαφυγών, 11,9% ποσοστό θνητότητας 30 ημερών, 7,6% ποσοστό εγκεφαλικών και 3,6% ποσοστό ισχαιμίας του νωτιαίου μυελού. Σχετικά με την τύπου II υβριδική προσέγγιση, μεταξύ 40 ασθενών, το ποσοστό ενδοδιαφυγών ήταν 12,5%, το ποσοστό θνητότητας 30 ημερών ή ενδονοσοκομειακής θνητότητας ήταν 5,3%, το ποσοστό εγκεφαλικών ήταν 2,5%, δε σημειώθηκε μόνιμη παραπληγία και το ποσοστό απώτερης θνητότητας ήταν 12,5%. Τέλος, 989 ασθενείς υποβλήθηκαν στην τεχνική «frozen elephant trunk». Το ποσοστό θνητότητας 30 ημερών ή ενδονοσοκομειακής θνητότητας (5.04% [95CI=1.13-10.74] ήταν χαμηλότερο συγκριτικά με αυτό της μελέτης των Μουλακάκη και συνεργατών που περιελάμβανε 1316 ασθενείς (9,5%). Σημειώθηκε ένα ακόμα χαμηλότερο ποσοστό εγκεφαλικών από αυτό της μελέτης των Μουλακάκη και συνεργατών (2.38% [95CI=0.13-6.30] έναντι 6,2%), καθώς και ένα χαμηλότερο ποσοστό μη αναστρέψιμης παραπληγίας λόγω ισχαιμίας του νωτιαίου μυελού (0.63% [95CI=0.00-2.73] έναντι 5%).

Συμπεράσματα

Οι τεχνικές υβριδικής αντιμετώπισης του αορτικού τόξου επεκτείνουν τις ενδείξεις της αντιμετώπισης των παθήσεων του αορτικού τόξου, ιδιαίτερα στους υψηλού κινδύνου ασθενείς που δεν είναι καλοί υποψήφιοι για ανοιχτή χειρουργική επέμβαση. Είναι μια ασφαλής εναλλακτική της ανοιχτής αποκατάστασης επιλογή με αποδεκτά βραχυ- και μεσοπρόθεσμα αποτελέσματα. Ωστόσο, τα ποσοστά εγκεφαλικών και θνητότητας παραμένουν αξιοσημείωτα. Χρειάζονται μελλοντικές προοπτικές μελέτες άμεσης σύγκρισης των ανοιχτών συμβατικών τεχνικών, με τις υβριδικές ή τις εξ’ ολοκλήρου ενδαγγειακές προσπελάσεις. Εργασίες με μεγαλύτερο αριθμό ασθενών και μακρύτερους χρόνους παρακολούθησης θα πρέπει να σχεδιαστούν πριν την εφαρμογή των υβριδικών προσπελάσεων και σε χαμηλού κινδύνου ασθενείς.

Λέξεις κλειδιά: υβριδικές τεχνικές, αορτικό τόξο, αποκλαδοποίηση, παγωμένη προβοσκίδα ελέφαντα

INTRODUCTION

Aortic aneurysms are diagnosed more and more frequently thanks to better imaging and screening tools. Twelve per cent of thoracic and thoracoabdominal aneurysms >6 cm will rupture without treatment in a year. Moreover, up to 50% of these patients will die within 5 years, if they only receive medical treatment.(1,2) However, the surgical management of patients with extensive aortic disease including the ascending aorta, the aortic arch, and the descending aorta is a technical challenge with a lot of place for innovations.(3,4) The gold standard of surgical therapy for patients with extensive thoracic aorta pathology is still the conventional elephant trunk technique, developed by Borst in 1983.(2,3,5,6) However, the conventional open surgical repair of aortic arch pathology is an invasive procedure, requiring cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA). As a result, open surgical repair of the aortic arch is related to significant morbidity and mortality rates. Furthermore, the older the patient is, the worse the results of open surgical repair are.(3,7-9) Even if there is complex circulatory management and adjunct cerebral protection nowadays, neurologic and cardiovascular complications leading to significant morbidity and mortality are high.(10) Brain, spinal cord, cardiac, visceral ischemia, and respiratory compromise due to prolonged circulatory arrest, should be avoided. Although there is noticeable progress in perioperative care, operative techniques, and the use of several protective adjuncts, total arch replacement (TAR) may lead to significant morbidity, such as air embolism, stroke, myocardial infarct, and excessive bleeding.(3) Despite advances in surgical techniques, anesthesia and intensive care management, reported mortality rates range from 7 to 17%, while rates of neurological injury range from 4 to 12%.(12-14) Moreover, some patients' medical status is not fit enough to undergo such a treatment and these patients deny surgery.(16) Consequently, alternative approaches related to better morbidity and mortality outcomes are required.(17,18)

On the other hand, endovascular repair of aortic aneurysms using stent grafts has become a practical alternative to open repair.(12) Endovascular stent grafting becomes more and more popular, since several studies showed feasibility and lower morbidity and mortality rates of endovascular treatment compared to open repair.(19-21) Endovascular aortic procedures are gradually replacing open surgical procedures.(18) An adequate landing zone of at least 20 mm is strongly required to perform endovascular repair.(2,18,22,23) Furthermore, a balance needs to be drawn between the morbidity of open surgery and the physiological reserves of the patient.(2) A hybrid approach is a combination of tools available only in the catheterization laboratory with those available only in the operating room in order to gain maximum profit from both of them.(18) In 1991, Volodos and colleagues were the first who performed hybrid aortic arch repair. Since that time, thoracic endografts have largely been incorporated into the treatment of aortic arch disease using hybrid approaches.(24) Hybrid approaches are an attractive alternative to TAR or total endovascular techniques for any given set of cardiovascular lesions.(18) The hybrid arch repair seeks to limit operative, bypass, and circulatory arrest times by making the arch repair procedure simpler and shorter.(17) Consequently, high-risk patients who are unsuitable for open repair can gain profit from hybrid procedures. These “hybrid techniques” include aortic arch debranching, thus creating an adequate proximal landing zone, followed by stenting over the aortic arch. The endovascular steps can be performed either simultaneously or in a staged mode, and in an antegrade or retrograde fashion. Frozen or stented elephant trunk approach (FET) is also a hybrid modification of Borst’s approach, in case of extensive aortic disease.(3)

The hybrid debranching thoracic endovascular aortic repair approach combining debranching of aortic arch vessels with thoracic endovascular aortic repair (TEVAR) of the aortic arch is a way to extend the envelope of intervention in aortic arch pathologies, particularly in patients with poor physiological reserves due to comorbidities, who are suboptimal candidates for open surgery.(2,10,26) Multiple studies have demonstrated the feasibility of this approach, related to acceptable mortality and morbidity rates.(27-29) The principal concept is reimplantation or bypass of aortic arch vessels to ensure a sufficiently long proximal landing zone and TEVAR implantation landing proximally in zone 0 which can be suitable for use as a landing zone either natively or artificially after ascending aorta replacement with a Dacron graft.(17) By hybrid debranching approach, operative, bypass, and circulatory arrest times are significantly shortened (17), but the problem of endovascular leaks comes to foreground. However, resolution of endovascular leaks in up to 90% of the cases is noted within 6 months.(18) On the other hand, FET was developed in the 1990s as a one-stage alternative to the conventional two-stage elephant trunk procedure for patients with extensive thoracic aortic disease.(4,30) Therefore, the need for a second procedure is minimized, as the risk of mortality between stages does.(4) A detailed review of the literature, published from January 2013 until December 2016, concerning hybrid aortic arch reconstruction procedures follows.

ISHIMARU AORTIC ARCH ZONES

Mitchell and Ishimaru (31) established the classification of aortic arch zones. The ascending aorta proximal to the innominate artery is named as Zone 0 whereas the innominate artery proximally and the left common carotid artery distally are the borders of Zone 1. The aortic arch between the left common carotid artery and the left subclavian artery is called Zone 2 and the proximal descending thoracic aorta distal to the left subclavian artery is Zone 3. Finally, Zone 4 involves the mid-descending thoracic aorta.(FIGURE 1) (3)

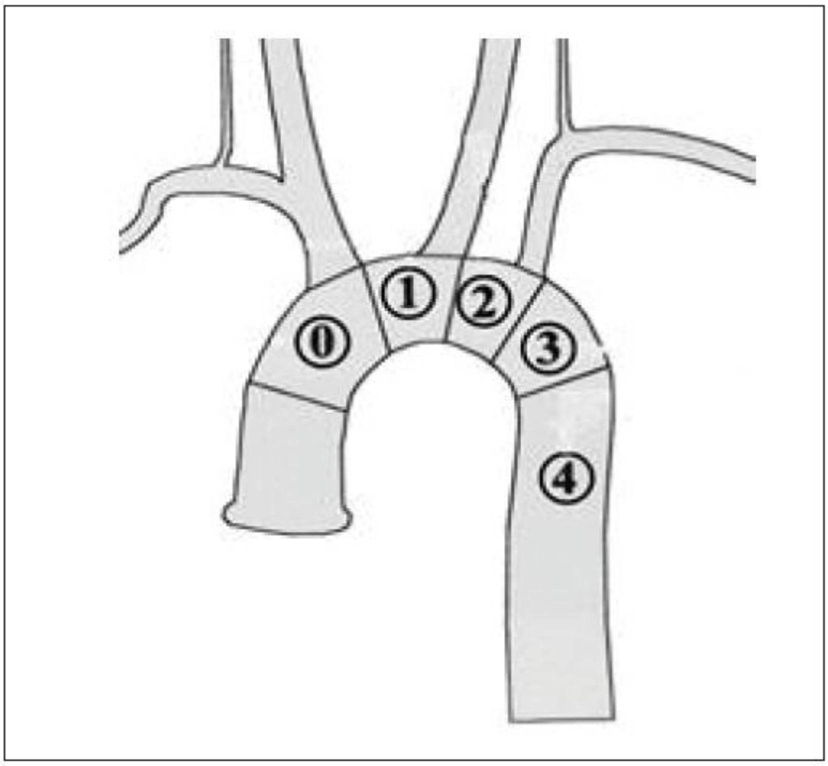

FIGURE 1. Ishimaru aortic arch Zones(32)

HYBRID AORTIC ARCH RECONSTRUCTION TYPES

The extent of aortic arch lesion and the presence of the proximal and distal landing zone indicate three types of hybrid aortic arch reconstruction: type I (debranching), type II (debranching along with ascending aorta reconstruction), type III (frozen elephant trunk).(FIGURE 2)

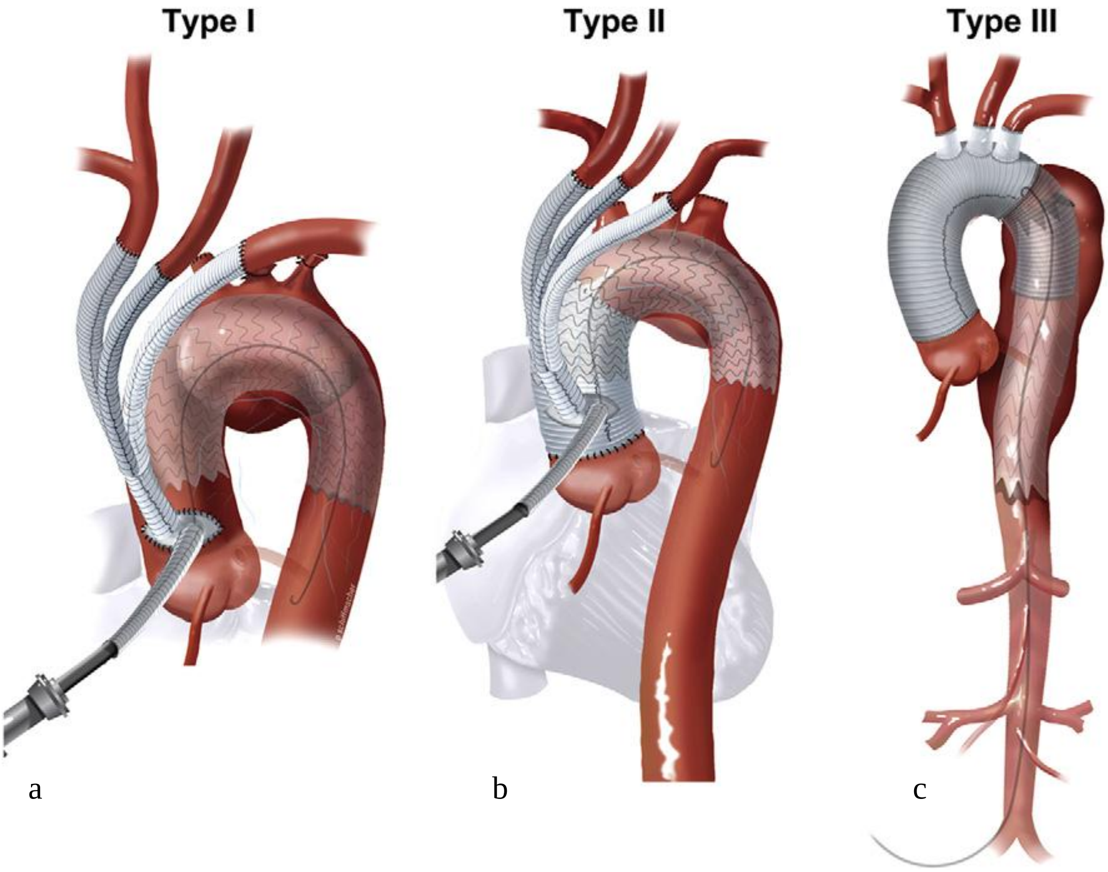

FIGURE 2. Hybrid aortic arch repair, types I, II, and III.(10)

- **Type I (debranching)**

The debranching hybrid approach involves total arch debranching and subsequent thoracic endovascular aortic repair and it entails an accepted strategy for high-risk patients requiring TAR.(33) An adequate proximal landing zone length is required for proper endovascular stent-graft deployment and stabilization.(21) Debranching of the head vessels creates an appropriate landing zone extending to Ishimaru Zone 0 without interrupting supra-aortic trunks perfusion.(34) A median sternotomy is performed to gain access to the ascending aorta and supra-aortic trunks which are mobilized. After full intravenous heparinization, a side-biting clamp is applied to partially clamp the ascending aorta as close to the aortic root as possible, leaving an adequate landing zone for the subsequent endovascular grafting.(FIGURE 3) Pharmacological lowering of the arterial blood pressure is of utmost importance during this maneuver.(35) An aorto-innominate graft can be placed first just distally to the sinotubular junction and then surgical revascularization is provided by reimplanting the head vessels to this graft.(9) Aortic arch vessels reimplantation can also be performed by a prefabricated four-branched Dacron graft sewn to the native ascending aorta just above the sinotubular junction.(FIGURE 2a)(17) The chosen graft is anastomosed to the greater curvature of the ascending aorta as close to the aortic root as possible in an end-to-side fashion.(15,35) No matter the graft which will be used, the innominate artery is anastomosed in an end to side fashion to the graft while flow to the right carotid artery is not interrupted for any period of time with the help of a small partial occlusion clamp. After the anastomosis has been performed, the innominate artery is ligated proximally. An end to end anastomosis approach is also possible if adequate cerebral oxygen saturation is present. Clamping the left carotid artery for three minutes without significant changes showing ischemia in the cerebral oxygen saturation is indicative for the next step of the procedure. The left carotid artery is ligated and transected at its origin and an end-to-end anastomosis is performed between the graft and the left common carotid artery.(FIGURE 2a, FIGURE 3) In the case of cerebral ischemia (meaning less than 60% of baseline left cerebral oxygen saturation), an intraluminal shunt with an end-to-side anastomosis in the neck is a choice. Finally, the left subclavian artery is proximally ligated or endovascularly occluded and anastomosed either directly to a limb of the graft already anastomosed to the ascending aorta,(FIGURE 2a, FIGURE 3)(35) or to the left carotid artery with a graft via a small supraclavicular incision.(FIGURE 4)(10,35) After each anastomosis, the graft should be flushed to eliminate any thrombus or air.(15) As far as type I hybrid reconstruction is concerned, there is no need for ascending aorta replacement. As a result, aortic cross-clamping and CPB can be avoided.(36) However, establishing CPB with or without a short aortic crossclamp time is also a reasonable approach.(10) When surgical revascularization of the supra-aortic trunks is complete, the second phase of stent-graft delivery and implantation into the transverse aortic arch under fluoroscopic guidance is performed.(FIGURE 2a, FIGURE 3, FIGURE 4)(9,35) The endovascular delivery and deployment of the graft can be done either antegradely through a fourth limb of the graft anastomosed to the ascending aorta,(Figure 2a)(37) or retrogradely through a common femoral artery.(35)

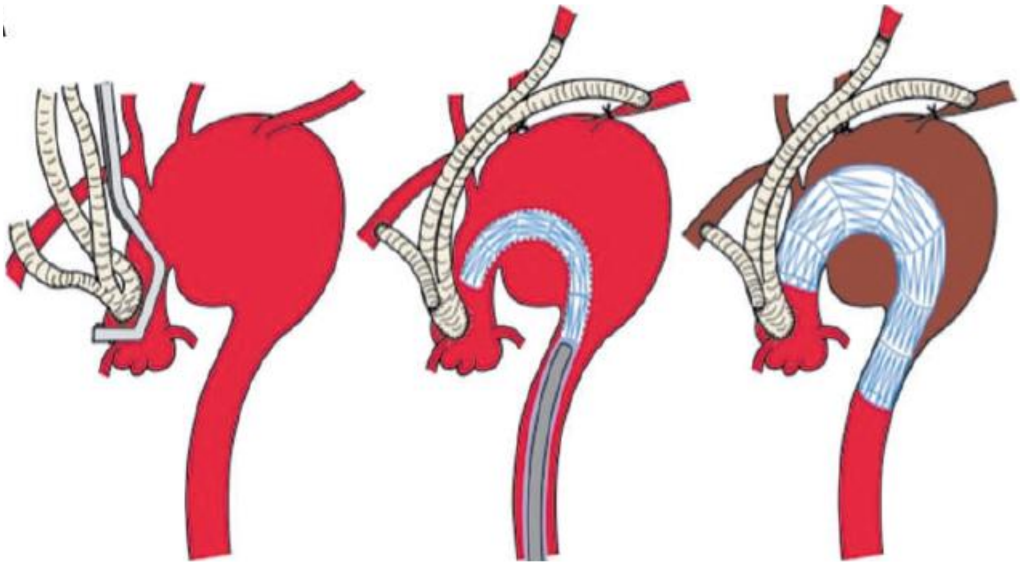

FIGURE 3. Type I hybrid aortic arch reconstruction. Debranching of the head vessels with partial clamping of the aorta and endovascular stent graft deployment into the aortic arch.(15)

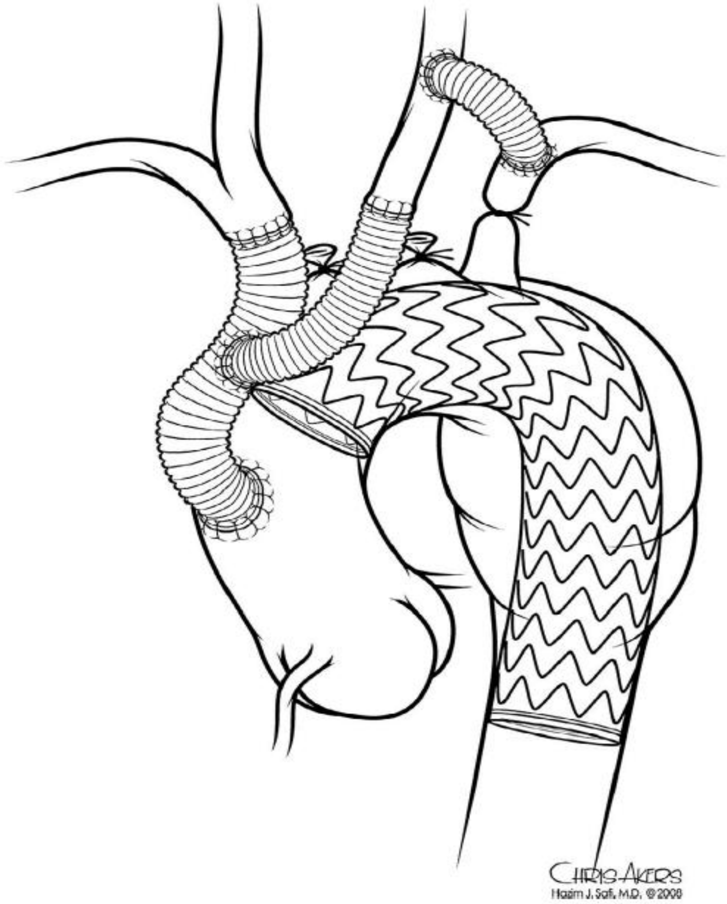

FIGURE 4. Left subclavian to left common carotid bypass, debranching of the innominate and left common carotid arteries and stent graft deployment into the aortic arch.(33)

- **Type II (debranching along with ascending aorta reconstruction)**

In case of an unsuitable proximal landing zone due to aneurysmal ascending aorta, replacement of the ascending aorta with a Dacron graft can be performed to serve as an artificially adequate landing zone for the endovascular stent-graft deployment.(FIGURE 2b, FIGURE 5a)(10,15,17) CPB and a short period of circulatory arrest for ascending aorta replacement under either retrograde or selective antegrade perfusion are required for the completion of type II arch hybrid operations.(10,17) After right axillary cannulation and median sternotomy, full heparinization and CPB are established. The distal ascending aorta is crossclamped and the proximal ascending aorta is then resected to the level of the sinotubular junction. If aortic root pathology is present, a valve-sparing or composite aortic root replacement may take place. Subsequently, the ascending aorta is replaced in an end-to-end fashion using a prefabricated 4 side-limbs tube Dacron graft designed for arch debranching.(FIGURE 6) After the distal ascending aorta anastomosis has been completed, sequential aortic arch debranching is performed on CPB with the crossclamp off. Each limb of the graft is sequentially anastomosed to the left subclavian artery or alternatively to the left axillary artery, to the left carotid artery and to the innominate artery.(FIGURE 5b) Weaning of CPB follows and the fourth limb of the graft is used for antegrade stent graft delivery.(FIGURE 7) Finally, the endovascular stent graft is deployed in an antegrade fashion from the ascending aorta to the proximal descending thoracic aorta.(FIGURE 5c, FIGURE 8)(38)

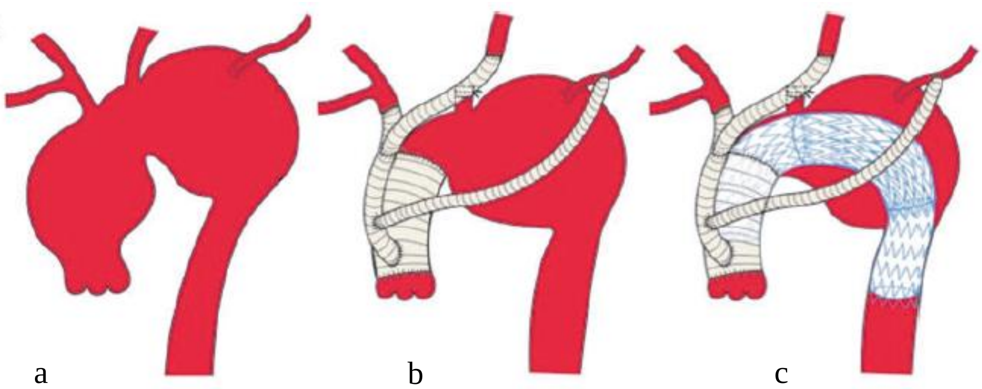

FIGURE 5. a.unsuitable proximal landing zone due to aneurysmal ascending aorta, b.replacement of the ascending aorta with a Dacron graft and sequential anastomosis of each limb of the graft to the left subclavian artery, to the left carotid artery and to the innominate artery, c. endovascular stent-graft deployment from the artificial Dacron ascending aorta to the proximal descending thoracic aorta.(15)

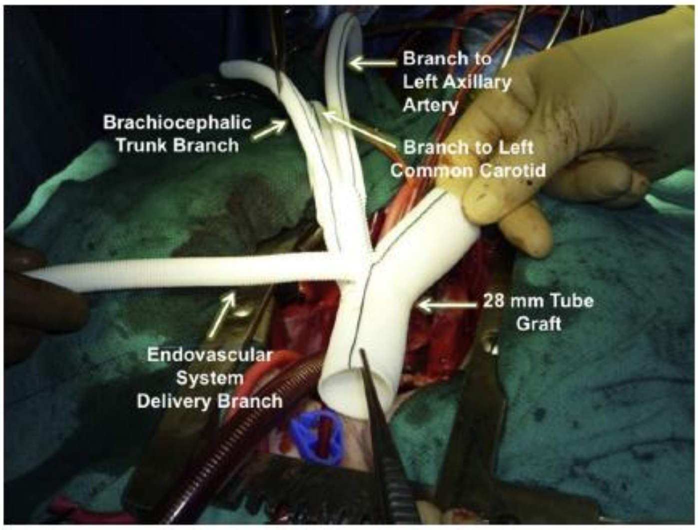

FIGURE 6. A prefabricated 4 side-limbs tube Dacron graft designed for arch debranching.(38)

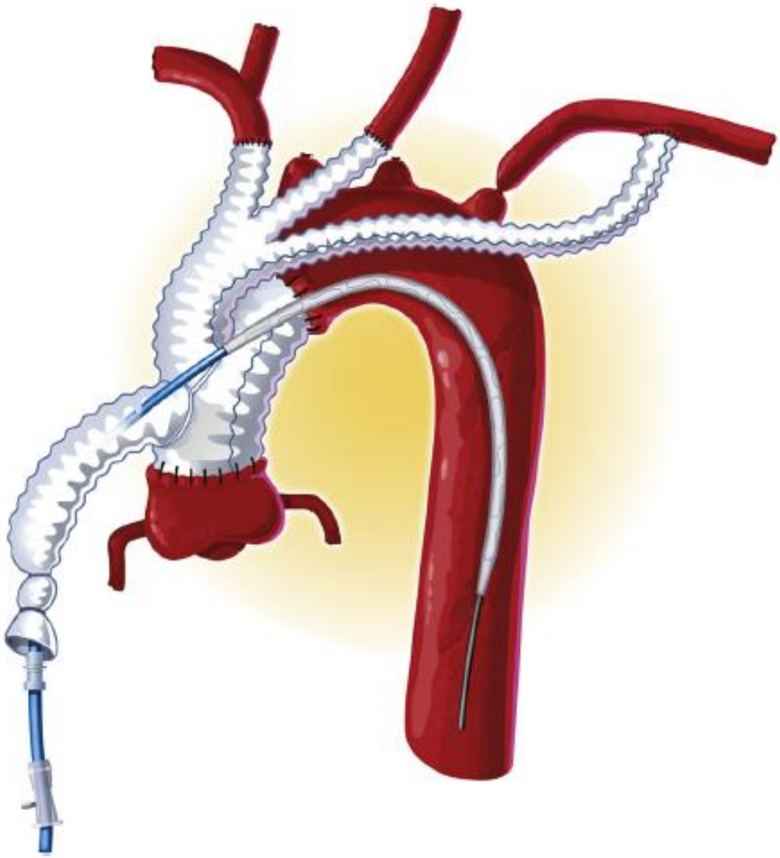

FIGURE 7. Antegrade delivery of the endovascular stent graft via the fourth limb of the graft.(38)

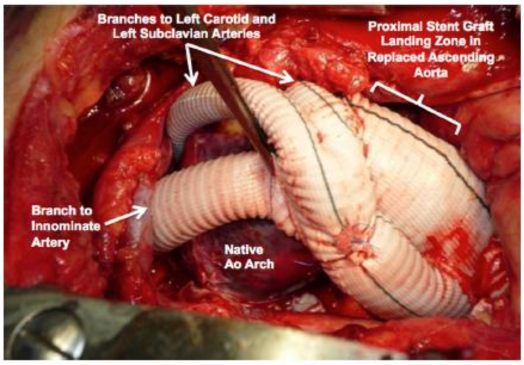

FIGURE 8. Completed arch debranching with stent deployed at Dacron zone 0.(38)

- **Type III (frozen elephant trunk)**

The FET procedure is a combination of the conventional open aortic arch repair with open endovascular treatment of the descending aorta in a single-stage procedure.(39) Kato (40) first described this modification of the conventional elephant trunk procedure with the deployment of a distal stent graft, whereas Karck (39) gave it the name “frozen elephant trunk”. Many variations of this approach has been described but its principal concept is delivery of the stent graft into the open aorta under circulatory arrest and suturing it into position.(FIGURE 2c)(41) The advantage is that the distal stented portion of the stent graft provides an anastomotic seal at the descending aorta due to expansive radial force.(4,41) However, type III hybrid arch repairs are not classic hybrid arch repair procedures. Circulatory arrest with either selective antegrade perfusion or a combination of antegrade and retrograde cerebral perfusion are required.(10,17) Right axillary artery cannulation for selective antegrade brain perfusion during circulatory arrest is preferred. After median sternotomy and full heparinization, CPB is established and the patient is cooled to 20^{o}C before circulatory arrest, while common femoral artery access is achieved. A 100-cm catheter is delivered and parked in the ascending aorta over a floppy hydrophilic guidewire under fluoroscopic guidance. Before the initiation of circulatory arrest, a graft for arch debranching is created if there is not a prefabricated one. Once adequate cooling has been achieved (proved by electroencephalographic silence), supra-aortic branches are clamped. Here starts the time of circulatory arrest and antegrade brain perfusion. A left arm pressure between 40 and 60 mm Hg is the goal, achieved by diminishing arterial flow to 750-1000 mL/min. The head is encircled by bags of ice. Additional left common carotid artery cannulation may be necessary in case of incomplete cervical or intracranial collateral circulation. The aorta between the sinotubular junction proximally and the aortic arch –most commonly between the origins of left carotid and left subclavian artery- distally is then transected, the aforementioned parked catheter is visualized and a stiff wire is delivered into the catheter. Next steps are the left subclavian artery transection at its origin and oversewing of its stump and the mobilization with buttons of aorta of the rest two head vessels. The supra-aortic vessels are sewn individually in an end-to-end fashion to the prefabricated graft or as an island. Clamps are removed, limbs are deaired and one clamp is applied more proximally to allow bicarotid cerebral perfusion. Subsequently, the aortic arch distal anastomosis (proximal end of stent graft) is performed.(30) Either a prefabricated covered stent sutured to the distal end of a conventional tube graft or a conventional endovascular stent distal to the arch graft under direct vision can be used.(4) The prepared stent graft is then antegradely implanted and deployed over the stiff wire into the descending aorta. The proximal end of the endograft should be placed at the level of the transected aortic arch.(FIGURE 9) Oversizing is usually not necessary at the proximal end as direct suturing of the conventional tube graft and the endovascular graft with the aortic wall ensures seal and fixation, whereas the rule of 10%-20% endovascular oversizing is applied for the distal landing zone. After stent graft deployment, the delivery system and the stiff wire are withdrawn after the insertion of an angiographic catheter over the wire. The surgical aortic graft, the stent graft, and the patient's native aorta are sutured altogether using a running 4-0 prolene suture to form the distal aortic anastomosis.(FIGURE 10) Next, the multibranched supra-aortic graft is sewn in an end-to-side fashion with a running 5-0 prolene-reinforced suture to the right great curvature of the surgical arch graft.(FIGURE 11) Finally, the clamp of the multibranched graft is removed, full flow is reestablished, the patient is rewarmed after normalization of metabolic parameters and a proximal end-to-end anastomosis to recreate the sinotubular junction is performed by a running 4-0 or 5-0 prolene suture. After the completion of the anastomosis, the aortic cross clamp is removed and the final aortogram is performed.(FIGURE 12) Weaning off CPB takes place and the patient is closed as it is used to be.(30)

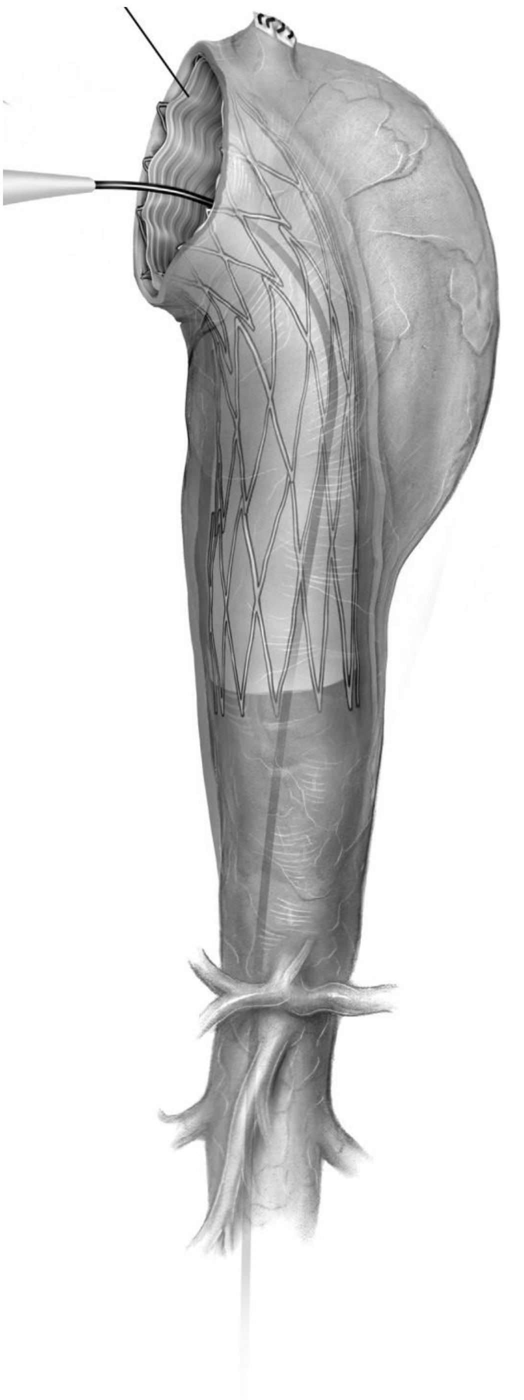

FIGURE 9. Stent graft is then antegradely implanted and deployed over the stiff wire into the descending aorta. The proximal end of the endograft should be placed at the level of the transected aortic arch.(10)

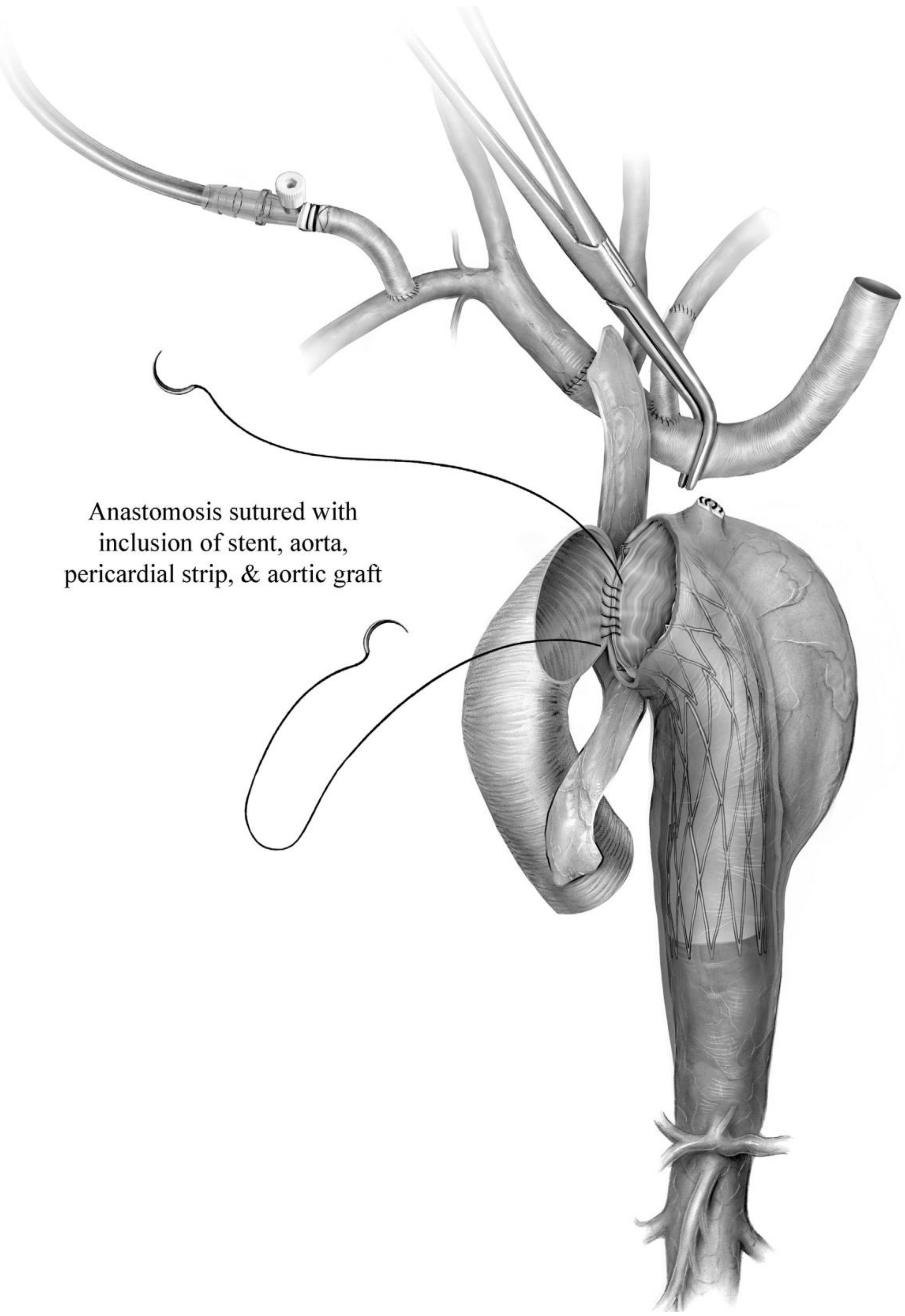

FIGURE 10. The surgical aortic graft, the stent graft, and the patient's native aorta are sutured altogether to form the distal aortic anastomosis.(10)

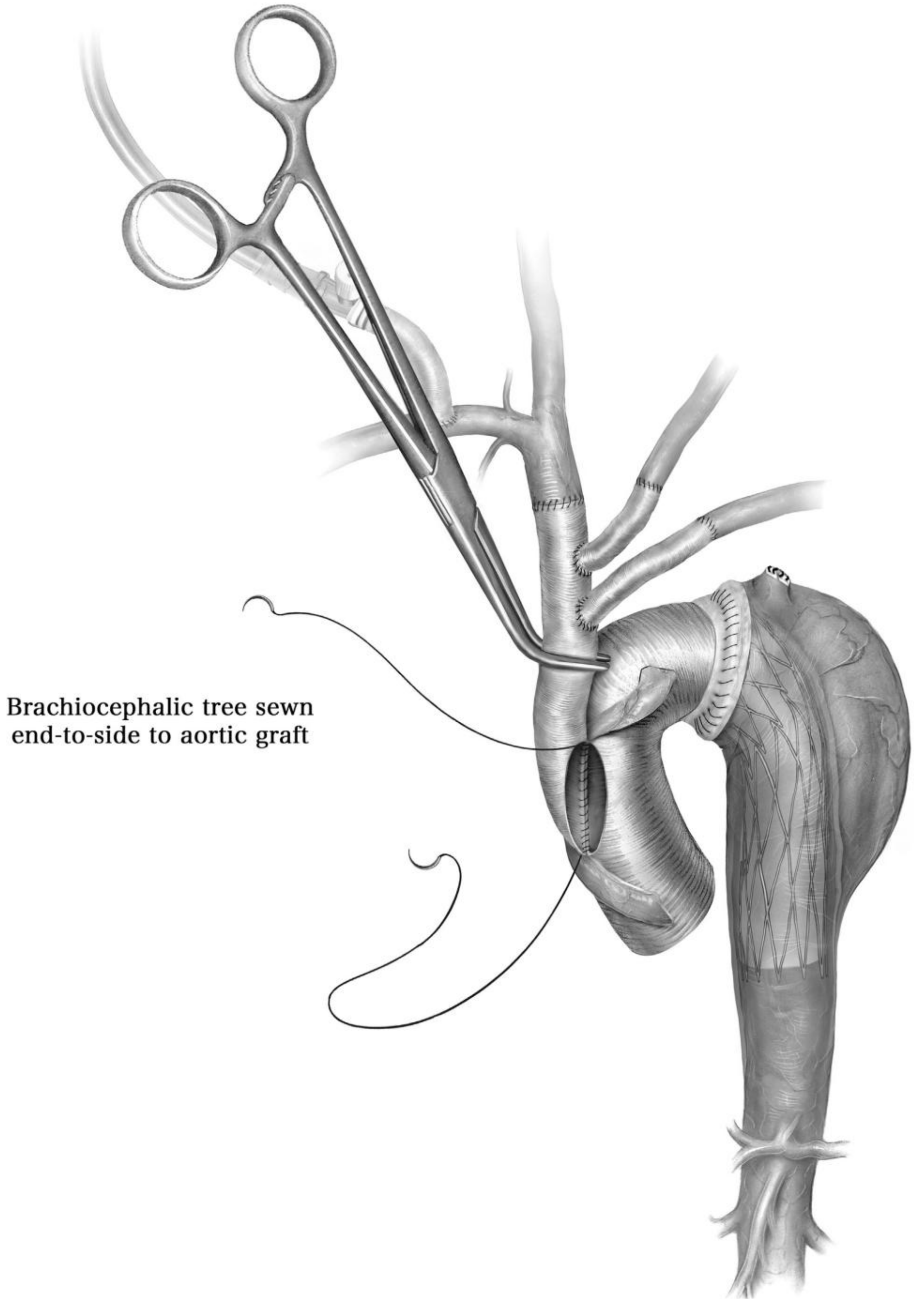

FIGURE 11. Multibranched supra-aortic graft sewn to the right great curvature of the surgical arch graft.(10)

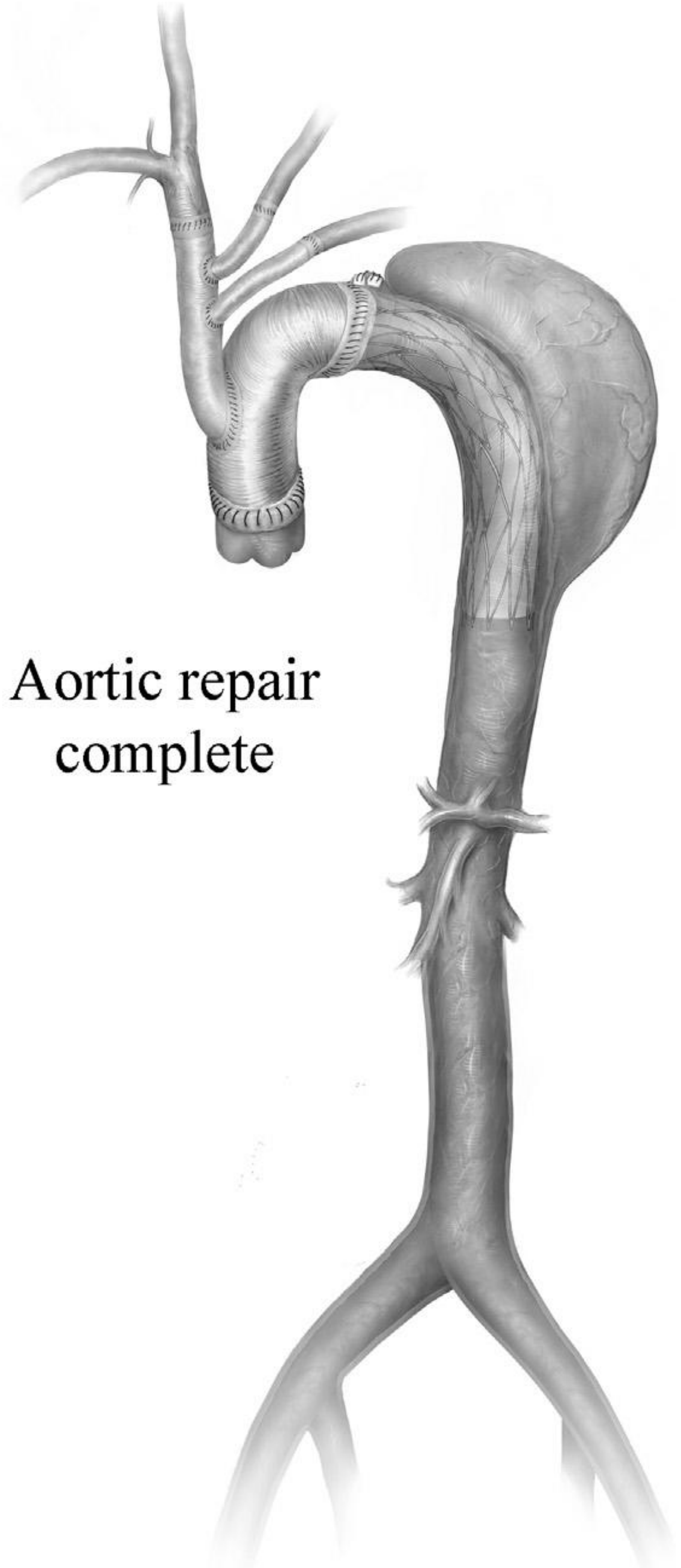

FIGURE 12. Complete aortic repair via frozen elephant trunk.(10)

AIMS OF THE STUDY

The aim of this study was to review the literature on hybrid aortic arch reconstruction of all three types published from January 2013 to December 2016 and to extract data for morbidity and mortality associated with these procedures. The base of this study was a meta-analysis by Moulakakis et al who analyzed hybrid aortic arch reconstruction studies up to December 2012.(3) The indications of each hybrid approach type are also analyzed as well as the main advantages or disadvantages of each procedure.

MATERIALS AND METHODS

An extensive electronic literature search was undertaken to identify all articles concerning hybrid aortic arch repair that were published from January 2013 up to December 2016. A meta-analysis including all articles concerning hybrid aortic arch repair up to December 2012 had already been published by Moulakakis et al in 2013. Provided that pooled results of studies before January 2013 had already been reported in the aforementioned meta-analysis, these studies were excluded from this review. The medical literature database "Pubmed" was systematically searched. Keywords used for the research were "aortic arch", "arch debranching", "frozen elephant trunk", "endovascular", and "hybrid". In addition, a snow ball process in the reference lists of the eligible articles was performed after retrieving the relevant articles from databases' search.

In the present review, eligible studies were categorized into three groups: group I, which included studies on total debranching of the aortic arch (type I hybrid aortic arch repair), group II, which included studies on total debranching of the aortic arch along with ascending aorta replacement (type II hybrid aortic arch repair) and group III, which included studies on the frozen elephant trunk procedure (type III hybrid aortic arch repair). Eligibility criteria were description of intrathoracic hybrid aortic arch repair, number of patients included equal to or over than 2, total aortic arch debranching in case of type I or type II hybrid procedures and the English language. Articles in languages other than English, case reports, and cases of partial aortic arch debranching were excluded. Studies with overlapping population were also excluded.

Data extracted from eligible studies included first author’s name and year of publication, study period, total number of patients, mean age, percentage of males, prior medical history, prior surgical history, indications for treatment, mean length of hospital stay (days) and follow-up (months). For patients submitted to type I hybrid procedure data on rate of off cardiopulmonary bypass procedures were extracted, whereas cardiopulmonary bypass time (minutes), aortic cross clamp time (minutes) and circulatory arrest time (minutes) were extracted from articles concerning frozen elephant trunk procedure.

Percentages of patients with outcomes of interest were also extracted. These included 1) technical success, 2) 30-day/in-hospital mortality, 3) stroke, 4) permanent paraplegia, 5) recurrent nerve palsy, 6) transient neurologic deficit or paraplegia, 7) renal failure and renal failure requiring dialysis, 8) respiratory insufficiency or prolonged ventilation, 9) retrograde aortic dissection, 10) atrial fibrillation or other cardiac event, 11) peripheral embolization or pulmonary embolism, 12) reoperation for bleeding, 12) endoleak, 13) late mortality, 14) cumulative survival at 1-year and 15) reoperation.

As far as the statistical analysis is concerned, STATA statistical software v14 (Stata Corp LP, USA) was used. Values of the studied outcomes were calculated, expressed as proportions and 95% confidence intervals (95% CIs) and thereafter transformed into quantities according to the Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled effect estimates were calculated as the back-transformation of the weighted mean of the transformed proportions, using DerSimonian-Laird weights of random effects model and expressed as % proportions. A formal statistical test for heterogeneity using the I^2 test was performed. Publication bias was assessed using the Egger's test for small-study effects, as well as visual inspection of funnel plots.

However, when the data extracted were scarce due to low number of studies which analyzed them, a meta-analysis would be weak, so the following mathematical formula was used instead to estimate the weighted average of each endpoint adjusted to the number of patients included in each study:

$$\text{Weighted average} = (n_1x_1 + n_2x_2 + \ldots + n_zx_z) / (n_1 + n_2 + \ldots + n_z)$$

n= total number of patients included in each study,

x= rate that each endpoint happened

INDICATIONS OF EACH HYBRID AORTIC ARCH RECONSTRUCTION TYPE

Although conventional surgical repair of aortic arch pathologies is the standard of care, hybrid aortic arch reconstruction approaches are less invasive alternatives in case of elderly, extensive comorbidities, concomitant malignancy or high-risk anatomical features such as previous cardiac surgery.(15) A contrast-enhanced computed tomography (CT) scan is necessary to estimate whether endoluminal repair is feasible, as well as the graft size to be used and the endovassular approach. A proximal aortic neck length of at least 20 mm is required for stent-graft placement required. Oversized from 10% to 20% is applied to achieve sufficient radial force for adequate fixation. Access vessels and supra aortic vessels are also preoperatively assessed by CT scan.(34) Stent implantation is either achieved retrogradely through a femoral/iliac conduit, or antegradely through the ascending aorta.(26) The position of the proximal end of the endovascular stent graft in the landing zone is critical for the success of the endovascular part of the procedure. A landing zone of at least 1.5 to 2 cm is recommended for secure endograft delivery.(42) Moreover, when the endovascular stent graft is deployed, maneuvers to lower cardiac output are highly recommended to prevent dislocation.(42)

An adequate landing zone in the ascending aorta and a distal landing zone in the descending thoracic aorta are the prerequisites for type I hybrid approach in patients with aortic arch aneurysms.(3) If the patient is hemodynamically stable with a not calcified aorta, the procedure is performed by partial clamping of the aorta without CPB, otherwise CPB with or without a short aortic cross-clamp time is established.(17,36) Type II hybrid approach is indicated for aneurismal pathologies of the ascending aorta extending into the distal arch.(3) In these cases, the ascending aorta is inadequate for zone 0 stent graft landing.(10,17,36) When the diameter of the ascending aorta is more than 4 cm, there is an increased hazard for a retrograde type A aortic dissection and for endovascular leak if type I hybrid approach is performed.(10,43) Consequently, in these cases, type I hybrid approach is inadequate. Instead, the aneurismal ascending aorta should be replaced, and the artificial ascending aorta should be used as landing zone for the stent graft and for the debranching graft transposition.(43) Finally, when an extensive aortic pathology affecting the ascending, transverse arch, and descending thoracic aorta or when “mega-aorta syndrome” is present, type III hybrid approach (FET) is the optimal hybrid approach.(3) In such cases, cerebrospinal fluid drainage may be used to prevent spinal cord ischemia in case of extensive aortic repair.(34)

REVIEW OF THE LITERATURE RESULTS AND META-ANALYSIS

As far as pure type I hybrid aortic arch reconstruction is concerned 11 studies were included. A total number of 122 patients were submitted to total aortic arch debranching according to these studies. Moulakakis’s meta-analysis included 26 studies, with a total of 956 patients, submitted to the aortic arch debranching procedure.(3) In the current study, males represented 55.8% of all the patients. Their weighted average age was 72.5 years old, whereas high rates of co-morbidities and prior surgical aortic or cardiac interventions were noted, thus classifying them as high-risk patients for conventional open aortic arch reconstruction. Aortic arch aneurysm was the most common indication for treatment.(table 1) Type I hybrid aortic arch reconstruction was performed without CPB in the majority of the cases. Weighted primary technical success was 97.5% in accordance with Moulakakis’s meta-analysis pooled rate of 92.8%.(3) However, the pooled endoleak rate was 10.78% (95%CI=1.94-23.40) (FIGURE 13) (5.2% weighted average of endoleak type I and 7% weighted average of endoleak type II). Moulakakis et al(3) reported a little higher rate of endoleaks (16.6%), the majority of which were type I. Follow-up ranged from 10.3 to 85 months. Several endpoints have been studied. The pooled 30-day or in-hospital mortality was 3.89% (95%CI=0.324-9.78) (FIGURE 14), even lower than the pooled mortality rate of 11.9% in Moulakakis’s study.(3) The pooled stroke rate was 3.79% (95%CI=0.25-9.77) (FIGURE 15) and the weighted permanent paraplegia rate was 2.4%, whereas transient neurologic deficit such as transient paraplegia affected 6.2% of the cases. Low rates of other complications, below 10% in the majority of studies, including renal failure requiring dialysis, respiratory insufficiency or prolonged ventilation, and reoperation for bleeding were reported. Retrograde type A aortic dissection ranged from 5.7% to 14%, although two small studies with less than 5 patients revealed no such a case. Similar results were extracted by Moulakakis’s meta-analysis where the pooled 30-day mortality rate for the “debranching” procedures was 11.9%, the stroke rate was 7.6%, the spinal cord ischemia rate was 3.6% and postoperative retrograde type A dissection was presented in 4.5% of the patients.(3) Furthermore, data analysis of this study proved that pooled reoperation rate during follow-up was 4.71% (95%CI=0.11-13.04) (FIGURE 16) whereas 14.17% (95%CI=0.73-35.49) was the pooled late mortality rate (FIGURE 17). Finally, the pooled cumulative survival at 1-year was quite high, 90.15% (95%CI=72.47-99.93) (FIGURE 18). Table 2 consists a detailed recording of mortality and morbidity related to hybrid type I procedures.

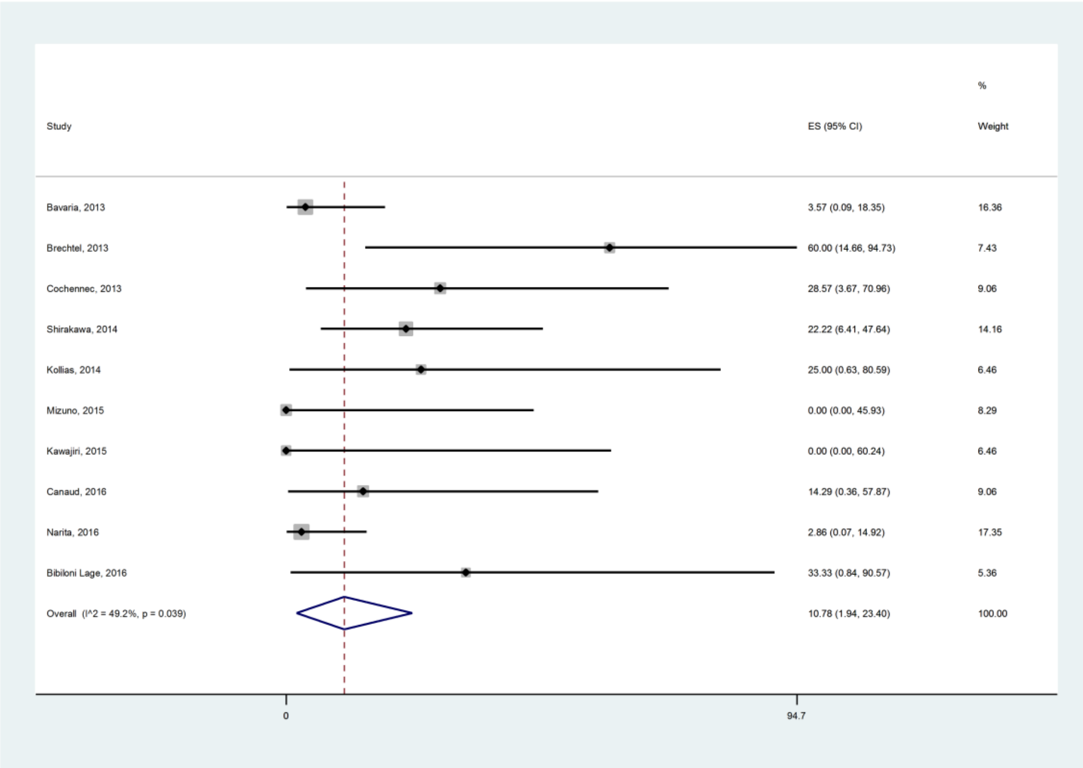

FIGURE 13. Forest plot presenting the meta-analysis of endoleak during follow-up based on event rates for hybrid type I studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

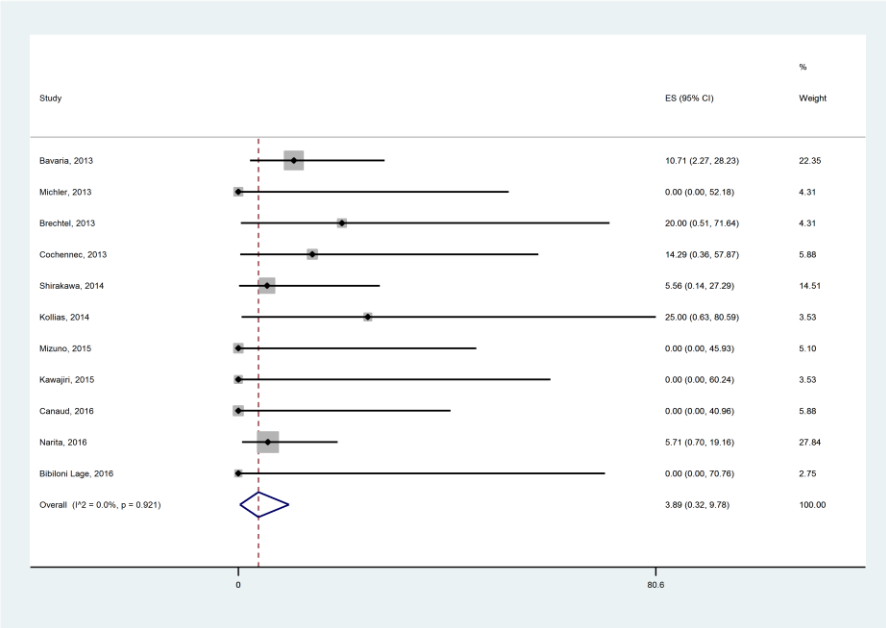

FIGURE 14. Forest plot presenting the meta-analysis of 30-day/in-hospital mortality based on event rates for hybrid type I studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

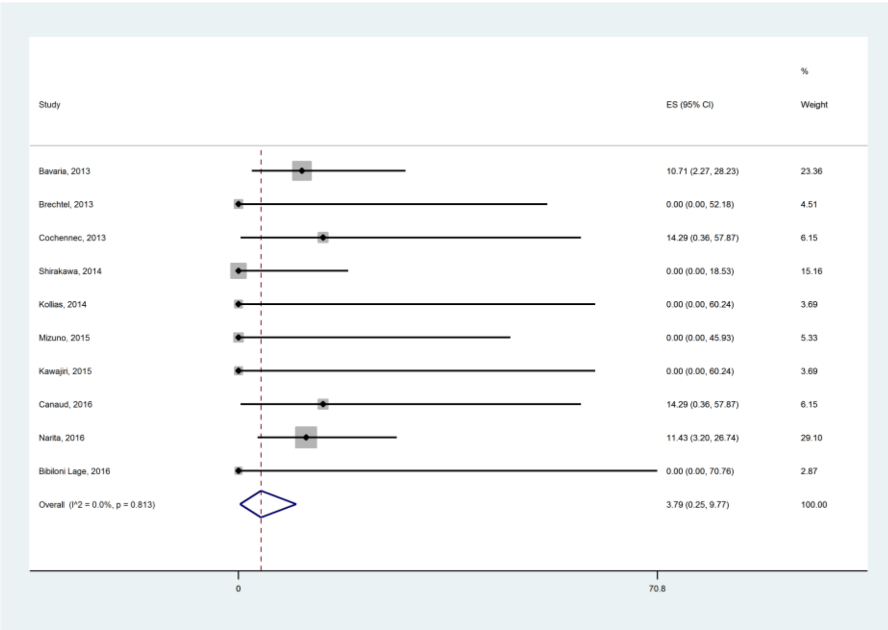

FIGURE 15. Forest plot presenting the meta-analysis of stroke based on event rates for hybrid type I studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

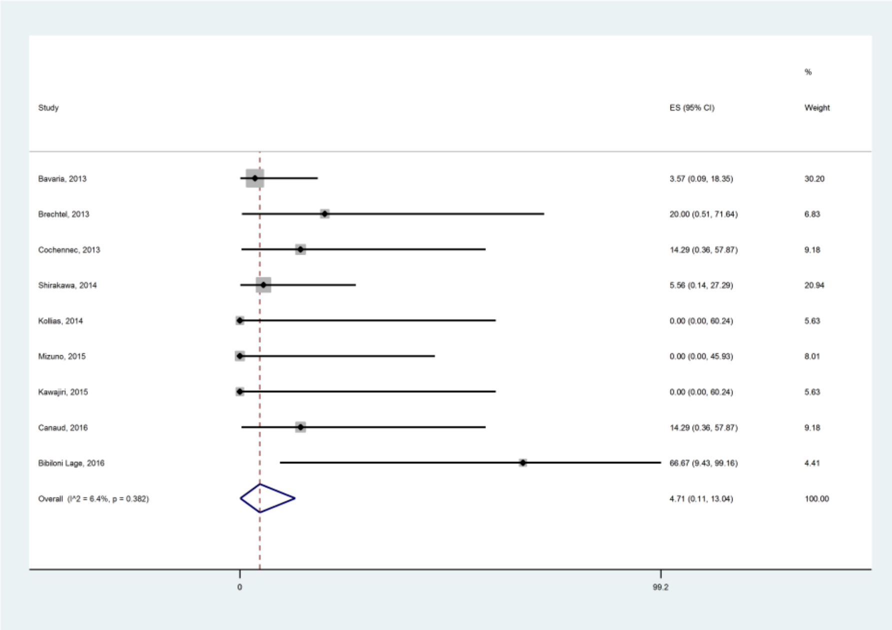

FIGURE 16. Forest plot presenting the meta-analysis of reoperation based on event rates for hybrid type I studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

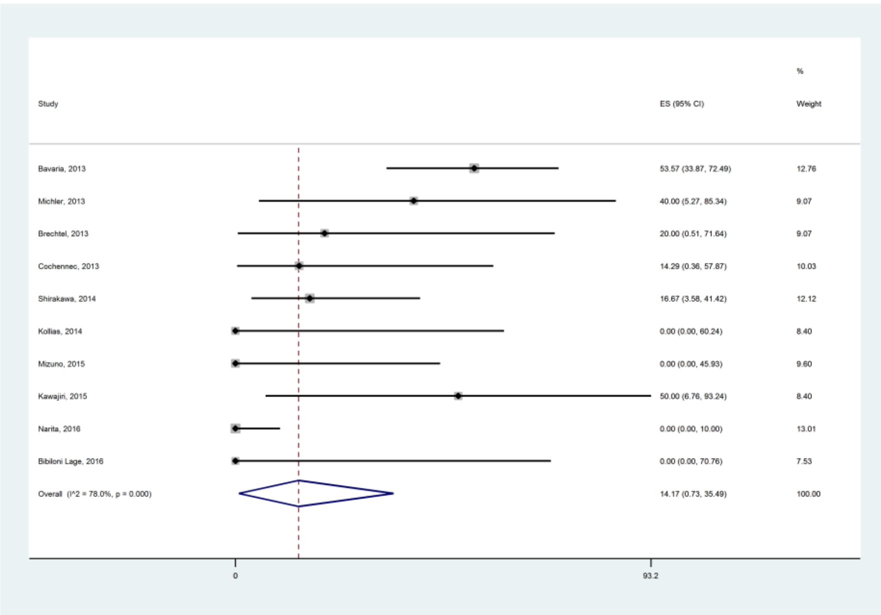

FIGURE 17. Forest plot presenting the meta-analysis of late mortality based on event rates for hybrid type I studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

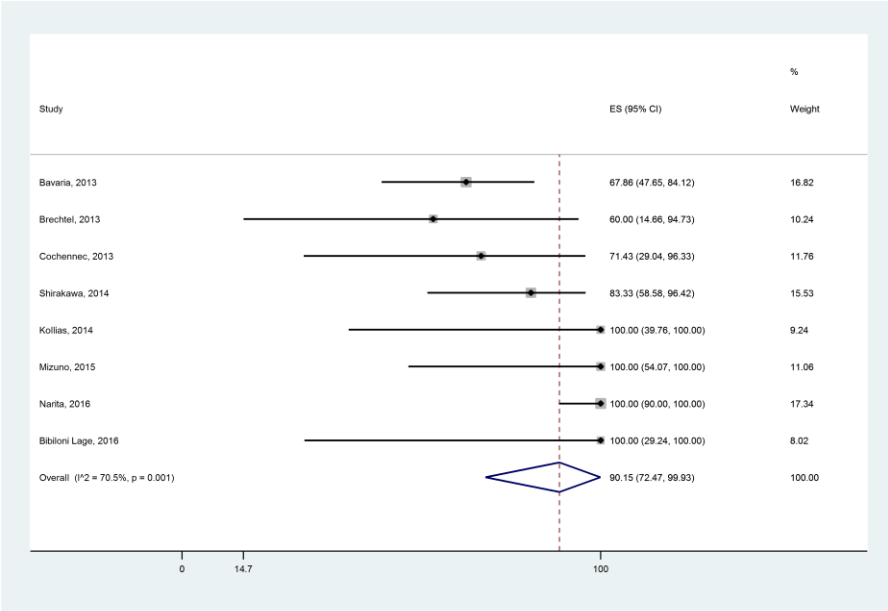

FIGURE 18. Forest plot presenting the meta-analysis of cumulative survival at 1-year based on event rates for hybrid type I studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

Table 1. Type I hybrid patients' characteristics

Study	Study Period	Total number of patients	Mean age (years)	Males (%)	Prior medical history	Prior surgical history	Indications for treatment	Off CPB (%)	Follow-up (months)
Bavaria (2013)(10)	2005-2012	28	70.7±8	64	42% prior stroke, 39% chronic lung disease, 32% prior myocardial infarction, 21% chronic renal insufficiency, 82% smoking	14% redo sternotomy, 7% coronary artery bypass grafting, 4% patent foramen ovale repair, 4% type A dissection repair, 4% thoracoabdominal aortic aneurysm repair, 4% prior thoracic aortic endograft, 14% abdominal aortic aneurysm (open or EVAR)	aortic arch aneurysm (89%), chronic aortic dissection (4%), aortic arch pseudoaneurysm (7%)	57	30±21
Michler (2013)-abs (44)	2008-2011	5	70.6±18	80	40% COPD, 40% coronary artery disease, 40% diabetes, 20% arrhythmia, 20% active angina, 20% cerebrovascular accident	20% aoric surgery for dissection	Nr	Nr	22±18.4
Brechtel (2013) (42)	2010-2011	5	75.2	20	Nr	60% supracomissural ascending aorta replacement-open distal anastomosis, 20% Supracomissural ascending aorta replacement-hemiarch replacement, 20% Bentall-hemiarch replacement	redo (100%), aortic arch aneurysm (60%), pseudoaneurysm (40%)	60	Nr
Cochennec (2013) (16)	2004-2011	7	60±12	71	100% hypertension, 43%	57% previous aortic surgery	aneurysmal degeneration	100	27.2

					smoking, 29% COPD, 14% diabetes, 14% coronart artery disease, 14% prior myocardial infarction, 14% chronic cardiac failure, 14% chronic renal failure		of type B aortic dissection involving aortic arch (100%)		
Shirakawa* (2014) (15)	1997-2012	40 *(total debranching in 18 pts)**	72.2±8.1**	67**	33% COPD, 22% cerebrovascular disease, 22% coronary artery disease, 22% concomitant malignancy, 17% chronic renal failure **	11% previous cardiac surgery**	aneurysm (77.5%), type B aortic dissection (10%), residual dissection after repairing type A aortic dissection (7.5%), aortic rupture (5%)	100**	15.4
Kollias (2014) (35)	2010-2012	4	73.75	25	100% hypertension, 100% dyslipidemia, 100% COPD, 75% peripheral vascular disease, 50% smoking, 25% valvular heart disease, 25% diabetes, 25% chronic renal failure	0% prior sternotomy, 25% abdominal aortic aneurysm repair	high risk for conventional open repair (Euroscore I/II: 36.66%/9.62 %)	100	23.7
Mizuno (2015) (43)	2012-2013	6	75±11	nr	Nr	Nr	Nr	50	14.2
Kawajiri (2015) (45)	2010-2013	4	72	75	50% hypertension, 50% cerebrovascular disease, 50% coronary artery disease, 50% atrial fibrillation, 25% hyperlipidemia, 25% diabetes, 25% atrial septal defect	25% abdominal aortic graft replacement	Kommerell diverticula with right aortic arch and aberrant left subclavian artery (100%)	Nr	19.5
Canaud (2016) (34)	2003-2014	7	62±11	86	43% chronic obstructive pulmonary disease, 29% hypertension, 29% Marfan syndrome, 29% stroke, 14% chronic renal failure, 14% coronary heart disease, 14% diabetes mellitus	57% Bentall procedure, 43% supracoronary ascending aortic replacement	dissecting aortic arch aneurysm (86%), aortic arch rupture (14%)	Nr	42±37
Narita (2016) (46)	2008-2014	35	78.5± 5.1	85.70 %	28.6% prior ischemic heart disease, 20% prior cerebrovascular disease, 5.7% renal insufficiency, 20% pulmonary disease	17.1% previous ascending aortic aneurysm	Nr	Nr	10.3±10.1
Bibiloni Lage (2016)* (47)	2006-2015	3**	66**	33**	100% hypertension, 66% chronic renal failure, 33% hyperlipidemia, 33% prior stroke**	66% ascending aorta replacement**	aortic arch aneurysm (100%)**	100**	85**

***:** Not all of the patients included received total arch debranching. All characteristics concern all the patients included except if ** is noted

****:** These characteristics concern only patients submitted to total debranching procedure

(nr: not reported; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack)

Table 2. Results after hybrid type I aortic arch reconstruction

Study	Technical success (%)	30-day/in-hospital mortality (%)	Stroke (%)	Permanent paraplegia (%)	Recurrent nerve palsy (%)	Transient neurologic deficit/ paraplegia (%)	Renal failure/ requiring dialysis (%)	Respiratory insufficiency/ prolonged ventilation (%)	Retrograde aortic dissection
Bavaria (2013) (10)	nr	11	11	7	Nr	11	11/4	nr	Nr
Michler (2013)-abs (44)	100	0	nr	Nr	Nr	nr	nr	nr	Nr
Brechtel (2013) (42)	60	20	0	0	0	20	nr	20	0
Cochennec (2013) (16)	nr	14	14	0	29	0	Nr	nr	14
Shirakawa* (2014) (15)	100**	0/6**	0**	0**	6**	0**	0**	6**	6**
Kollias (2014) (35)	100	25	0	0	Nr	0	nr	nr	Nr
Mizuno (2015) (43)	nr	0	0	0	Nr	0	nr	nr	Nr
Kawajiri (2015) (45)	100	0	0	0	0	0	25	nr	0
Canaud (2016) (34)	100	0	14	0	Nr	14	nr	nr	Nr
Narita (2016) (46)	100	0/5.7	11.4	Nr	2.9	nr	5.7	nr	5.7
Bibiloni Lage (2016)* (47)	100**	0**	0**	0**	0**	0**	0**	0**	20

Study	Atrial fibrillation/ cardiac event (%)	Peripheral embolization/ pulmonary embolism (%)	Reoperation for bleeding (%)	Endoleak (%)	Late mortality (%)	Cumulative survival at 1-year (%)	Reoperation rate (%)
Bavaria (2013) (10)	39	nr	4	4 (type II)	53.6	68 (55% at 3 years)	4
Michler (2013)-abs (44)	nr	nr	Nr	Nr	40	Nr	Nr
Brechtel (2013) (42)	20	nr	0	60 (type Ia; n=2, type II; n=1)	20	60	20
Cochennec (2013) (16)	nr	14	0	29 (type II)	14	67	14
Shirakawa (2014) (15)	11	0	0	23 (type II; n=3, type Ia; n=1)	15	85 (74% at 3 years)	6
Kollias (2014) (35)	nr	nr	0	25 (type I)	0	100	0
Mizuno (2015) (43)	nr	nr	Nr	0	0	100	0
Kawajiri (2015) (45)	nr	nr	Nr	0	50	nr	0
Canaud (2016) (34)	nr	nr	Nr	14 (type I)	nr	nr	14 (2nd stent graft)
Narita (2016) (46)	nr	nr	Nr	2.9 (typeII)	0	100	Nr
Bibiloni Lage (2016) (47)*	0**	20	0**	33** (type Ib)	0**	100**	66**

***:** Not all of the patients included received total arch debranching. The results mentioned concern all the patients included except if ** is noted

****:** The result concern only patients submitted to total debranching procedure

(nr: not reported; postop: postoperatively)

In terms of debranching of supra-aortic trunks along with ascending aorta replacement (type II hybrid procedure), thorough data are included in tables 3 and 4. Four relevant studies were included examining 40 patients. The majority of them were males, whereas the weighted mean age was 70.2 years old. Accompanying co-morbidities and prior surgical history indicated these patients as high risk patients for conventional surgery, similarly to the patients received type I hybrid procedure. Aortic arch aneurysm was once again the most common indication for treatment.(table 3) Follow-ranged from 10 to 30 months depending on the study.

Primary technical success was 100% in all cases, although the weighted average of endoleak rate was 12.5%, similar to the aforementioned group, corresponding to 7.5% type I endoleak and 5% type II endoleak. Bibiloni Lage's study included only two patients submitted to type II hybrid aortic reconstruction, one of whom died in-hospital.(47) The average 30-day or in-hospital mortality of the other studies(15,17,38) containing over than 8 high-risk patients was noteworthy low (5.3%). Stroke average was only 2.5% and no permanent paraplegia was noticed, whereas 7 patients (17.5%) suffered from transient neurologic deficit or paraplegia. Only one patient presented renal failure requiring dialysis, whereas respiratory complications rate (in terms of respiratory insufficiency or prolonged intubation) was remarkably high (over than 10%). Six patients were reoperated for bleeding in the early postoperative period whereas only two patients were reoperated during follow-up. Finally, the weighted late mortality rate was 12.5% whereas cumulative survival rate was over 74% in the two studies(15,17) in which it was estimated. A thorough analysis of results of type II hybrid procedure studies are written in table 4.

Table 3. Type II hybrid patients' characteristics

Study	**Study Period**	**Total number of patients**	**Mean age (years)**	**Males (%)**	**Prior medical history**	**Prior surgical history**	**Indications for treatment**
Vallabhajosyula (2013) (17)	2005-2013	8	71.1±8.3	63	75% smoking, 38% prior cerebrovascular accident, 38% chronic lung disease, 38% prior myocardial infarction	13% redo sternotomy, 13% coronary artery bypass grafting, 13% prior thoracic aortic endograft, 38% abdominal aortic aneurysm (open or EVAR)	aortic arch aneurysm (63%), chronic aortic dissection (37%)
Kent (2014) (38)	2007-2012	20	67.05±16.86	nr	95% hypertension, 40% chronic lung disease, 40% cerebrovascular disease, 40% smoking, 15% renal failure, 10% diabetes	30% previous sternotomy	diffuse atherosclerotic aneurysm involving the arch (45%), penetrating atherosclerotic ulcer with contained rupture localized to the arch (10%), arch pseudoaneurysm at proximal extent of existing stent graft (10%), acute type A aortic dissection with intimal tear involving the arch (20%), chronic type B dissection with associated aneurysm involving the arch and descending thoracic aorta (15%)
Shirakawa (2014) (15)	1997-2012	40 *(type II hybrid in 10 pts)*	75.2±7.7**	70**	20% cerebrovascular disease, 20% coronary artery disease, 20% chronic renal failure, 10% COPD **	10% previous cardiac surgery**	aneurysm (77.5%), type B aortic dissection (10%), residual dissection after repairing type A aortic dissection (7.5%), aortic rupture (5%)
Bibiloni Lage (2016) (47)	2006-2015	2**	73.5**	50**	100% hypertension, 50% chronic renal failure, 50% hyperlipidemia, 50% diabetes on insulin, 50% smoking**	50% TEVAR and aortic valve replacement, 50% TEVAR**	chronic type A aortic dissection (50%), acute type A aortic dissection (50%)**

***:** Not all of the patients included received type II hybrid approach. All characteristics concern all the patients included except if ** is noted

****:** These characteristics concern only patients submitted to type II hybrid approach

(nr: not reported; COPD: chronic obstructive pulmonary disease)

Table 4. Results after hybrid type II aortic arch reconstruction

Study	Technical success (%)	30-day/in-hospital mortality (%)	Stroke (%)	Permanent paraplegia (%)	Recurrent nerve palsy (%)	Transient neurologic deficit/ paraplegia (%)	Renal failure/requiring dialysis (%)	Multiorgan failure with respiratory insufficiency/prolonged intubation (%)
Vallabhajosyula (2013) (17)	nr	0	0	0	nr	25	0/0	Nr
Kent (2014) (38)	100	10	5	0	nr	25	0	15
Shirakawa (2014)* (15)	100**	0**	0**	0**	10**	0**	0**	10**
Bibiloni Lage (2016)* (47)	100**	50**	0**	0**	50**	0**	50**	50**

Study	Atrial fibrillation/ cardiac event (%)	Retrograde aortic dissection (%)	Peripheral embolization (%)	Reoperation for bleeding (%)	Endoleak (%)	Late mortality (%)	Cumulative survival at 1-year (%)	Reoperation rate (%)	Follow-up (months)
Vallabhajosyula (2013) (17)	50	nr	Nr	0	0	12.5	87% (at 1 and 3 years)	0	30±21
Kent (2014) (38)	Nr	nr	Nr	25	15 (typeI), 5 (type II)	nr	nr	10	17.5
Shirakawa (2014)* (15)	0**	0**	10**	0**	10 (type II)**	15	85 (74% at 3 years)	0**	15.4**
Bibiloni Lage (2016)* (47)	20	nr	20	50 (for cardiac tamponade) **	0**	0**	nr	0**	10**

***:** Not all of the patients included received type II hybrid approach. The results mentioned concern all the patients included except if ** is noted

****:** The result concern only patients submitted to type II hybrid approach

(nr: not reported; COPD: chronic obstructive pulmonary disease)

Last, the third group of studies included in this review was that of patients submitted to the elephant trunk procedure. Moulakakis's meta-analysis included 20 studies, with a total of 1316 patients submitted to type III hybrid aortic arch reconstruction.(3) The current study included 13 studies with a total number of 989 patients. Patients included in this group (where this was mentioned) were younger than the other groups of patients were (mean age ranged from 59 to 72.3 years old). The majority of them were once again males. Significant co-morbidity rates and high percentages of previous cardiac or aortic surgery were also noted. Most common indications for treatment was acute aortic type A dissection.(table 5) Mean hospital stay was over 17 days in the vast majority of the studies and the follow-up period ranged from 10.3 to 42 months. Despite the severity of the pathologies, the pooled 30-day or in-hospital mortality rate was 5.04% (95CI=1.13-10.74) (FIGURE 19), which was a little lower compared to Moulakakis's meta-analysis(3) (9.5%). This is a quite acceptable outcome. An even lower than in Moulakakis's study(3) pooled rate of stroke was reported (2.38% [95CI=0.13-6.30] vs 6.2%) (FIGURE 20), as well as a lower weighted rate of irreversible paraplegia due to spinal cord injury (0.63% [95CI=0.00-2.73] vs 5%) (FIGURE 21). Renal failure requiring dialysis also occurred less common (10.9% vs 19.7%). A noteworthy weighted reoperation for bleeding rate (7.5%) was reported, which was similar to the 8.6% reported by Moulakakis et al.(3) Finally, the pooled cumulative survival at 1 year was remarkably high (86.7%, 95CI=81.08-92.90) (FIGURE 22). Table 6 includes all outcomes concerning hybrid aortic reconstruction type III.

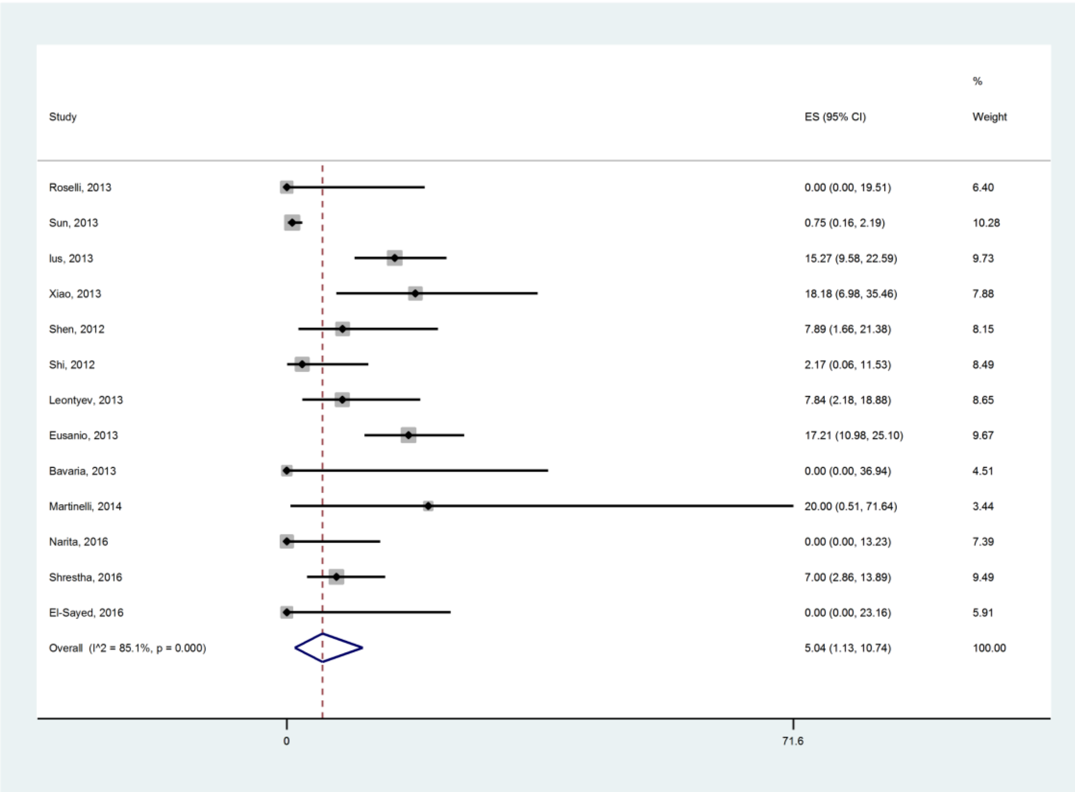

FIGURE 19. Forest plot presenting the meta-analysis of 30-day/in-hospital mortality based on event rates for hybrid type III studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

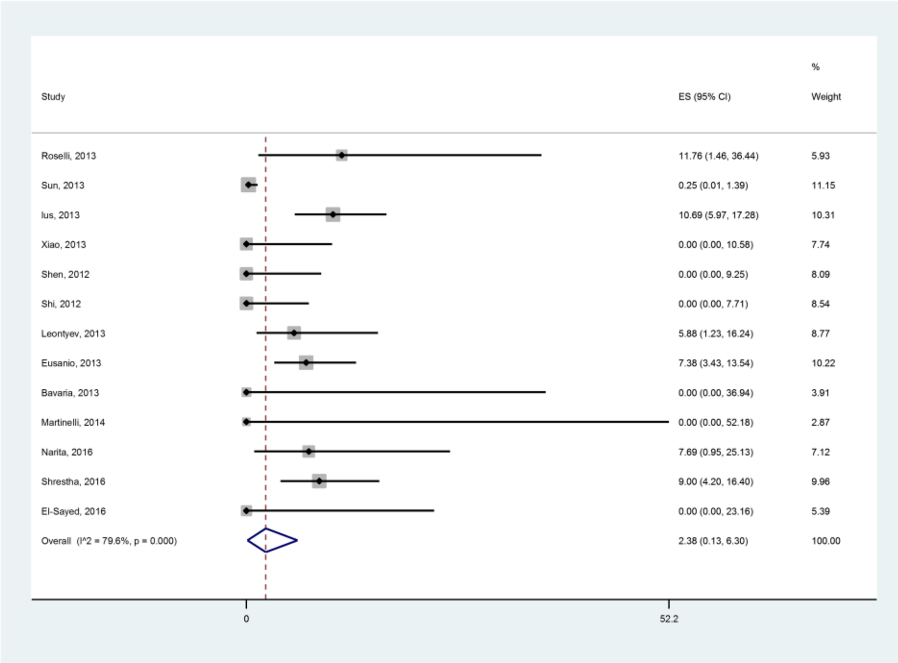

FIGURE 20. Forest plot presenting the meta-analysis of stroke based on event rates for hybrid type III studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

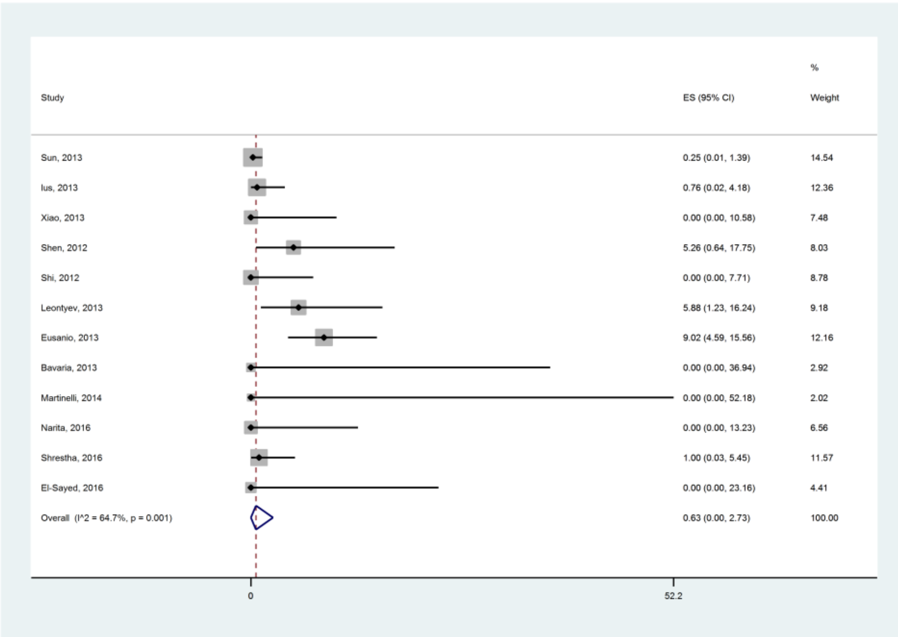

FIGURE 21. Forest plot presenting the meta-analysis of irreversible paraplegia based on event rates for hybrid type III studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

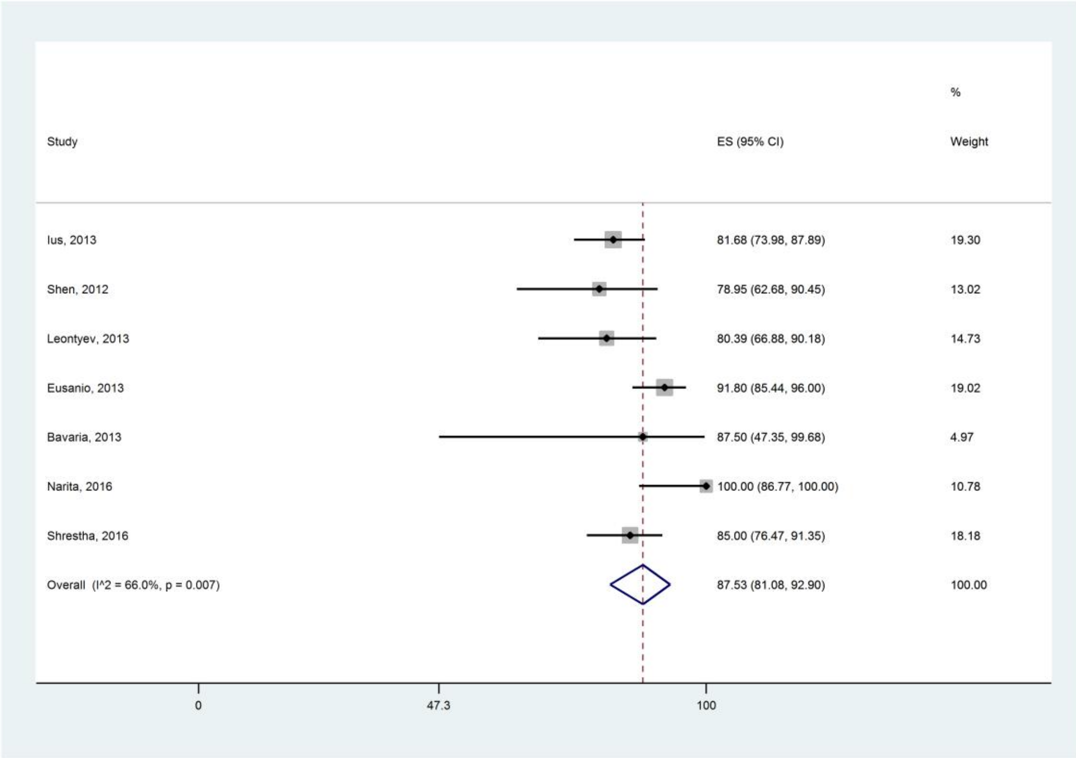

FIGURE 22. Forest plot presenting the meta-analysis of cumulative survival at 1-year based on event rates for hybrid type III studies included. Event rates in the individual studies are presented as squares with 95% confidence intervals (CIs) presented as extending lines. The pooled event rate with its 95%CI is depicted as a diamond.

Table 5. Frozen elephant trunk patients' characteristics

Study	Study Period	Total number of patients	Mean age (years)	Males (%)	Prior medical history	Prior surgical history	Indications for treatment
Roselli (2013) (4)	2009-2012	17	Nr	Nr	nr	Nr	acute type A dissection (100%)
Sun (2013) (4)	2003-2012	398	Nr	Nr	nr	Nr	acute type A dissection (100%)
Ius (2013) (4)	2001-2002	131	Nr	Nr	nr	nr	acute type A dissection (34%), chronic type A dissection (25%), acute type B dissection (2%), chronic type B dissection (8%), aneurysm (3%)
Xiao (2013) (4)	2008-2011	33	Nr	Nr	nr	Nr	acute type A dissection (100%)
Shen (2012) (4)	2010-2010	38	Nr	Nr	nr	Nr	acute type A dissection (100%)
Shi (2012) (4)	2007-2010	46	Nr	Nr	nr	Nr	acute type A dissection (100%)
Leontyev (2013) (6)	2006-2013	51	69±10	48.9	52.9% hypertension, 17.6% diabetes, 11.8% COPD, 3.9% cerebral vasculopathy	17.6% previous surgery (11.8% thoracic aorta, 5.9% valve, 2% CABG, 2% root, 2% abdominal aorta)	degenerative aneurysm (62.7%), acute type A aortic dissection (15.7%), acute type B aortic dissection

							(13.7%), downstream aneurysm following acute Type A aortic dissection (3.9%), chronic type A aortic dissection (2%), chronic type B aortic dissection (2%),
Eusanio (2013) (48)	2007-2012	122	61±10	86.9	86.9% hypertension, 15.6% COPD, 9% coronary artery disease, 5.7% cerebral vasculopathy, 2.5% renal insufficiency, 2.5% diabetes	56.6% previous cardiac/ aortic surgery	residual type A chronic dissection (45.9%), degenerative aneurysm (27%), chronic type B aortic dissection with associated proximal aneurysm (14.8%), acute type A aortic dissection (7.4%), chronic type A aortic dissection (4.1%), acute type B aortic dissection (0.8%)
Bavaria (2013) (10)	2005-2012	8	71.1±8.3	63	38% prior stroke, 38% chronic lung disease, 38% prior myocardial infarction, 0% chronic renal insufficiency, 75% smoking	13% redo sternotomy, 13% coronary artery bypass grafting, 13% prior thoracic aortic endograft, 38% abdominal aortic aneurysm (open or EVAR)	aortic arch aneurysm (63%), chronic aortic dissection (38%)
Martinelli (2014) (49)	nr	5	Nr	Nr	nr	nr	acute aortic dissection (60%), chronic aortic dissection (20%), degenerative aneurysm (20%)
Narita (2016) (46)	2008-2014	26	72.3 ± 7.9	80,1	30.8% prior ischemic heart disease, 19.2% prior cerebrovascular disease, 26.9% renal insufficiency, 15.4% pulmonary disease	34.6% previous ascending aortic aneurysm repair	Nr
Shrestha (2016) (50)	2010-2014	100	59±14	65	17% renal insufficiency, 12% Marfan syndrome, 11% malperfusion	28% previous surgery	acute dissection (37%), chronic dissections (31%), aneurysm (32%)
El-Sayed (2016) (51)	2013-2015	14	66±6	64	71% hypertension, 36% COPD, 29% aortic valve regurgitation	nr	ascending and distal arch aneurysm (57%), ascending, arch and descending aortic aneurysm (43%)

(COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass grafting; nr: not reported)

Table 6. Results after frozen elephant trunk

Study	CPB time (min)	Cross clamp time (min)	Ciculatory arrest time (min)	30-day, in-hospital mortality (%)	Stroke (%)	Permanent paraplegia (%)	Transient neurologic deficit (%)	Renal failure/ requiring dialysis (%)
Roselli (2013) (4)	Nr	nr	nr	0	11.8	nr (SCI)	Nr	5.9
Sun (2013) (4)	Nr	nr	nr	7.8	2.5	2.5 (SCI)	Nr	4.3
Ius (2013) (4)	Nr	nr	nr	15.3	10.7	0.8 (SCI)	Nr	16
Xiao (2013) (4)	Nr	nr	nr	18.2	0	0 (SCI)	Nr	3
Shen (2012) (4)	Nr	nr	nr	7.9	0	5.3 (SCI)	Nr	0
Shi	nr	nr	nr	2.2	0	0 (SCI)	Nr	Nr

(2012) (4)								
Leontyev (2013) (6)	213±66	98±38	50±14	7.8	11.8 (along with permanent paraplegia)	11.8 (along with stroke)	9.8	25.5
Eusanio (2013) (48)	237±64	153±48	64±18	17.2	7.4	9	Nr	24.6
Bavaria (2013) (10)	259±44	121±63	19±10	0	0	0	25	0/0
Martinelli (2014) (49)	Nr	nr	nr	20	0	0	0	20
Narita (2016)(46)	Nr	nr	nr	0	7.7	0	3,3	Nr
Shrestha (2016)(50)	243±61	101±65	51±20	7	9	1	6	30/14
El-Sayed (2016) (51)	214±35	125±14	54±9	0	0	0	14	Nr

(CPB:cardio pulmonary bypass; min: minutes; nr: not reported; SCI:spinal cord injury)

Study	Respiratory failure/ prolonged ventilatuion	Reoperation for bleeding (%)	Mean hospital stay (days)	Endoleak (%)	Late mortality (%)	Cumulative survival at 1-year (%)	Reoperation rate (%)	Follow-up (months)
Roselli (2013) (4)	nr	nr	20±12	nr	nr	nr	Nr	Nr
Sun (2013) (4)	nr	2.5	Nr	nr	nr	nr	Nr	Nr
Ius (2013) (4)	nr	18.3	18±17	nr	nr	82 (72% at 5 years)	Nr	42
Xiao (2013) (4)	nr	nr	26±11	nr	nr	nr	Nr	27
Shen (2012) (4)	nr	0	21±13	nr	nr	91	Nr	12
Shi (2012) (4)	nr	4.3	19±6	nr	Nr	nr	Nr	14
Leontyev (2013) (6)	37.3	13.7	nr	nr	Nr	80.2±5.5 (59.7±10.2% at 5 years)	17.6 (8/9 TEVAR)	40.8±4.8
Eusanio (2013) (48)	28.7	12.3	15	nr	10.7	91.7±2.8 (79.1±6.1)% at 3 years)	23.8	Nr
Bavaria (2013) (10)	nr	0	22.0±9.6	0	13	87	0	30±21
Martinelli (2014) (49)	0	nr	Nr	nr	Nr	nr	Nr	Nr
Narita (2016) (46)	nr	nr	14,7*	26.9 (type II)	0	100	Nr	10.3±10.1*
Shrestha (2016) (50)	29	10	17	nr	13	85	22	37.2±16.8
El-Sayed (2016) (51)	nr	0	9±2	nr	nr	nr	Nr	Nr

(nr: not reported)

CONCERNS ABOUT EACH APPROACH

➢ Disadvantages of conventional open aortic arch repair

Open aortic arch restoration procedure can be performed either by the two-stage elephant trunk approach or by a one-stage open repair via clamshell incision.(35) However, remarkable morbidity and mortality accompany these procedures in high-risk patients, in spite of the advanced cerebral protection perfusion strategies.(8,52) Although the classic elephant trunk procedure(5) is the standard of care for extensive disease of the thoracic aorta,(4) long periods of DHCA to reduce cerebral and end-organ dysfunction are required, so it is related to high risk for neurologic complications.(34,38) Long periods of circulatory arrest result in higher risk for stroke and visceral ischemia, whereas deep hypothermia is related to coagulopathy and subsequent higher risk for bleeding from the distal anastomosis.(38) Even short periods of circulatory arrest have a detrimental effect to higher cognitive function. The longer DHCA, the higher the incidence of cerebral and other end-organ injury.(34)

- **Pure endovascular problems**

It seems reasonable that endovascular treatment is associated to lower morbidity and mortality rates compared to open repair, as CPB with cerebral protection and aortic cross-clamping can be avoided.(34) However, the origin of the supra-aortic cervical vessels from the aortic arch constricts the application of total endovascular procedures.(34,35) Up to 30% endoleak incidence is reported,(53,54) due to lack of adaptability of commercially available stent grafts in the aortic arch and due to short landing zone.(16) A sealing zone of at least 2 cm of healthy native aorta is required to prevent endoleaks.(15,16) Angulation, risk of dissection, and the intolerance of supra-aortic vessels to any complications hamper the success of total endovascular aortic arch repair.(33)

- **Advantages of hybrid approach Type I**

Debranching hybrid approach type I is a single-stage procedure that can be performed without CPB, thus avoiding DHCA and its subsequent complications.(35) This lack of global cerebral circulatory arrest is the major advantage of hybrid type I approach.(33) Moreover, aortic cross clamping is avoided, thus reducing renal and visceral ischemia.(2) Myocardial dysfunction due to cardioplegia delivery is also avoided, as there is no need for cardiac perfusion interruption. Furthermore, phrenic or recurrent laryngeal nerve injury and pulmonary complications associated with bilateral thoracosternotomy approach are avoided.(33) Finally, even if access to femoral arteries is impossible due to severe peripheral vascular disease, the endograft can be antegradely delivered through the ascending aorta.(35)

- **Disadvantages of hybrid approach Type I**

The Achilles' heel of hybrid type I approach is neurologic complications.(10) A relatively high risk of stroke and endoleaks is reported, let alone that concomitant cardiovascular procedures cannot be performed in a single stage.(23) The benefits gained from avoiding DHCA, may be compensated by atheromatous or air embolism caused by manipulation of the supra-aortic branches and of the wires used.(33) Atherosclerotic disease is a predictor of perioperative stroke.(10) The more central the pathology of the thoracic aorta, the higher the risk of stroke.(55,56) The risk of stroke due to atheroembolization is increased during endograft delivery across a diseased aortic arch.(56) Soft plaques may be detached from the aortic wall during the manipulation of the wires in the aortic arch.(26,34) Although higher rates of endoleaks associated to hybrid debranching procedures have been reported with, a good resolution up to 90% at 6 months has been noticed.(9) Degeneration of the native ascending aorta may result in aneurysm formation or late type 1 endoleak.(33) Type Ia endoleak is reported in 15% to 30% of cases.(38) Another devastating complication caused by instrumentation of the aortic arch during both the debranching and endovascular portions of the procedure is retrograde aortic dissection.(33) Tangential clamping of the aorta, alterations in hemodynamics, lack of conformability between the stent graft and the native aorta and excessive radial forces at the aortic arch curvature are to put the blame on.(16,33) According to the European Registry on Endovascular Aortic Repair Complications, acute retrograde type A dissection incidence is 6% and the associated mortality rate reaches 42%.(38)

- **Advantages of hybrid approach Type II**

Type I hybrid approach is applicable only in the absence of aneurysmal ascending aorta that is suitable landing zone for the endograft.(35) If a stent graft is deployed in a dilated native ascending aorta, type IA endoleak, rupture, pseudoaneurysm formation, and retrograde type A dissection are potential complications.(38) Flat, straight, long, and cylindrical landing zones are optimal for stable deployment of endografts. As a consequence, if the ascending aorta is replaced, the risks of retrograde type A dissection and endoleak are eliminated. Furthermore, hybrid type II approach is a less-invasive total arch reconstruction strategy that is associated with less bleeding related to open arch replacement under deep hypothermia and lower risk of stroke thanks to eliminating the need for circulatory arrest.(38)

- **Advantages of hybrid approach Type III**

By applying this approach, aortic arch aneurysms extending to the descending aorta can be repaired in a single stage procedure under circulatory arrest.(3) The most important series (17-21) concerning the conventional elephant trunk procedure have shown a mortality rate up to 25% during the interval between the two stages, mostly due to aortic rupture. FET, performed in one stage, avoids this interval mortality.(48) The keypoint of the procedure is direct suturing of the endograft to the aorta and the surgical aortic graft providing with the security of fixation and eliminating the risk of endoleak type I.(3,41) The radial expansion of the stent-graft prevents from anastomotic leakages and eliminates the risk of kinking and flapping of the prosthesis. As far as aortic dissection is concerned, intimal tears of the descending aorta are sealed thanks to the compression of the false lumen and expansion of the true lumen, thus preventing further dilation of the proximal descending aorta.(4)

- **Disadvantages of hybrid approach Type III**

According to International E-Vita open Registry, FET is related to higher mortality and brain injury rates compared to more conservative management, because of the need for the use of CPB and DHCA.(35,48) Spinal cord injury is a possible complication due to inflammatory response because of the great extent of the operation and due to covering a large aortic segment.(4,30) Consequently, there is an increased risk for paraplegia.(48) According to the International E-vita Open Registry including 274 patients, spinal cord injury happened in 8.0% of them.(57,58) In spite of partial resolution of paraparesis and paraplegia in 40% of patients, significant complications persisted.(4) On the other hand, permanent or transient spinal cord injury is a rare complication after conventional elephant trunk procedure, ranging from 0.4% to 2.8%.(6) Circulatory arrest, coverage of intercostal arteries, embolization, and postoperative hypotension are potentially responsible for spinal cord injury after FET procedure.(48) A distal landing zone of T7 or lower, abdominal aortic aneurysm repair history and a core body temperature equal to or over 28°C during circulatory arrest combined with circulatory arrest time over 45 minutes are strong predictors of spinal cord injury.(6,49) Consequently, deep hypothermia should be established when FET is performed, particularly in cases of prolonged aortic arch surgery.(6) Continuous total brain perfusion with cannulation of the left subclavian artery, lower body perfusion to reduce the duration of circulatory arrest, preventive cerebrospinal fluid drainage, and a mean postoperative arterial pressure over 80 mmHg are additional helpful measures to avoid these complications.(30,48,49) However, paraplegia will affect some of the patients despite applying these measures.(48)

COMPARISON OF HYBRID PROCEDURES WITH OPEN AORTIC ARCH REPAIR

Hybrid aortic arch repair procedures cannot be directly compared to open TAR due to selection bias, as high risk patients, usually elderly with significant comorbidities, who cannot receive open repair are potential candidates for a hybrid approach.(33,35) Hybrid aortic arch repair procedures extend the envelope of intervention with regard to complex aortic arch pathology management.(35) In spite of the open surgical techniques evolution, open arch repair remains an invasive approach. Mortality rates between 7% and 17% are reported, and 15% to 17% of patients require a skilled nursing facility or an inpatient rehabilitation unit after discharge from hospital.(15) Milewski et al, comparing open aortic arch repair to hybrid approach, revealed neither significant difference in terms of overall in-hospital mortality (16% vs 11% respectively) nor significant difference with regard to transient neurologic complications (11% transient cerebral neurologic deficit vs 11% transient, reversible, spinal cord ischemia respectively). Overall permanent neurologic complications were not significantly different either (9% vs 13% respectively). Moreover, new postoperative renal insufficiency and new postoperative hemodialysis requirement rates were similar between the 2 cohorts. However, after age stratification, the hybrid group had superior results. Although older age did not play a significant role in terms of in-hospital mortality in the hybrid group, its role in the open repair group was significant. Patients aged less than 75 years old were related to a 9% mortality whereas, older ones over than 75 year old were related to a 36% mortality. Consequently, patients over 75 years old had an in-hospital mortality up to 36% after open arch repair, which was significantly higher than the 11% mortality reported after hybrid arch procedures.(7) In overall the primary benefit of hybrid procedures is obvious in high-risk patients and particularly in the elderly over 75 year old with complex aortic arch pathology, such as large saccular aneurysms or mega-aorta syndrome, who have been excluded for receiving conventional open TAR.(7)

CONCLUSIONS

High-risk patients with complex aortic pathologies can gain profit from hybrid treatment. Hybrid procedures extend the indication for the patients who are unsuitable for open aortic arch repair.(26) Hybrid arch approaches are a safe alternative to open repair with acceptable short- and mid-term results.(3) However, stroke and mortality rates remain noteworthy.(3,26) Hence, currently, hybrid procedures are only an alternative to conventional open aortic arch surgery for the treatment of aortic arch pathologies and cannot replace the latter.(26) Hybrid one-stage aortic arch debranching without CPB, avoiding the need for circulatory arrest is an attractive and promising new approach for the treatment of high-risk patients with extensive aortic arch aneurysms.(26,35) In addition, FET offers the possibility of a single-stage operation for extensive aortic arch pathology repair.(4) FET is related to a relatively low mortality in patients with extensive thoracic aorta pathology. However, increased rates of postoperative permanent paraplegia due to spinal cord injury are reported, particularly if mild hypothermia (≥28 °C) and prolonged circulatory arrest times (≥45 minutes) are employed.(6) In conclusion, future prospective trials directly comparing open conventional techniques with hybrid or total endovascular approaches are required.(3) In terms of hybrid arch repair series, larger cohorts with longer follow-up should be planned before applying these approaches to low-risk patients.(15)

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APPENDIX

- *cm: centimeters*
- *CABG: coronary artery bypass grafting*
- *COPD: chronic obstructive pulmonary disease*
- *CPB: cardiopulmonary bypass*
- *CT: computed tomography*
- *DHCA: deep hypothermic circulatory arrest*
- *EVAR: endovascular aortic repair*
- *FET: Frozen elephant trunk*
- *min: minutes*
- *nr: not reported*
- *postop: postoperatively*
- *SCI: spinal cord injury*
- *TAR: total arch replacement*
- *TEVAR: thoracic endovascular aortic repair*
- *TIA: transient ischemic attack*