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State of the Art ASD Closure Devices for Congenital Heart

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Abstract

The purpose of this review is to describe the current state of the art in terms of available devices and indications for the transcatheter device closure of atrial septal defects (ASD) and patent foramen ovale (PFO) in children and young adults. Techniques for transcatheter device closure of ASD (TC-ASD) are well established and TC-ASD has a proven track record of efficacy and safety. Device erosion, a rare but potentially catastrophic adverse event of TC-ASD has raised questions about the relative safety of TC-ASD versus operative open heart surgical ASD closure (O-ASD). Despite a concerted effort to study the issue, there are no solutions that avoid the risk of erosions definitively when using the Amplatzer device. There is evidence that concern about erosions has changed practice in the United States, specifically that more patients are referred for O-ASD than in the past. Efforts to study these changes have also revealed more variation in TC-ASD practice than previously appreciated. New devices for ASD closure with properties that may reduce the risk of erosion are being developed and brought to market, but, in the meantime, cardiologists must continue to balance the risks and benefits of TC- and O-ASD closure. Recent studies demonstrating the superiority of PFO device closure over medical therapy for cryptogenic stroke is likely to lead to changes in practice for structural/interventional cardiologists. Previously, the overwhelming majority of ASD closure procedures were performed for right heart volume overload due to left to right shunt, but stroke prophylaxis may become a more significant part of the volume in pediatric/congenital catheterization laboratories. Care should be taken in extrapolating this data to children and younger adults, and important questions about patient selection remain unresolved.

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Keywords

erosion; pediatric cardiology; transcatheter intervention; outcomes

Current Devices for TC-ASD:

With an incidence of 6 to 10 per 10,000 live births[1], ostium secundum atrial septal defects (ASD) are one of the most common forms of congenital heart disease. King and Mills developed the first device for transcatheter closure of ASD (TC-ASD) in 1976[2]. The history of device development for TC-ASD is a testament to innovation in the field of congenital/structural cardiology[3]. Over time, TC-ASD has become the predominant technique for closing most ASD; >80% of isolated ASD treated at primary pediatric hospitals in the United States are closed in the catheterization laboratory[9].

At the present time, two devices for TC-ASD are widely available in the United States (Figure 1): the Amplatzer Septal Occluder (ASO) (St. Jude Medical, St. Paul MN) (Figure 1A and Figure 2) and the Gore Cardioform device (W.L. Gore and Associates, Flagstaff, AZ) (Figure 1B). The ASO was the first device approved by the FDA for TC-ASD demonstrating safety and efficacy in a non-randomized IDE trial[4], which was reinforced in a subsequent multicenter registry study[5]. It has been in use long enough for several large single-center case series to report excellent medium and long-term outcomes[6–8]. In contemporary case series of US centers, the ASO is used in between 70–86% of cases [9,10].

The Gore Helix Septal Occluder (W.L. Gore and Associates, Flagstaff, AZ) has also demonstrated excellent safety and efficacy in both short[11–13] and middle term outcomes[14]. The Helix Septal Occluder has been replaced by the Gore Cardioform device and is no longer sold in the US. The Cardioform device has a Nitinol wire frame covered with an expanded tetrafluoroethylene membrane. Like the Helix before it, this device was not self-centering and limited to relatively small defects. The initial device trial and continuing access series are complete with manuscripts pending at this time. Gore has produced a second Cardioform device – the Cardioform Atrial Septal Defect Occluder (C-ASDO)-with a larger diameter central waist and an expanded range of diameters, both designed to facilitate closure of larger diameter ASD's (Figure 1C and Figure 3). The newer C-ASDO device is currently undergoing an FDA Pivotal trial (Gore ASSURED Trial; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02985684) Identifier NCT02985684) in the United States. In a multicenter series from Canada, both Gore devices have demonstrated similar safety and efficacy to previous devices[15]. The Amplatzer multi-fenestrated septal occluder (“Cribiform” device) (St. Jude Medical, S t. Paul, MN) resembles the ASO device but has symmetric discs and a narrow waist, designed to allow it to cover the septum of patients with multiple defects.

Device Erosion of the Amplatzer Septal Occluder device:

Erosions of the device following TC-ASD with the Amplatzer device were first reported in a series of case reports in 2003 and 2004[16–18]. Alarm about erosions was particularly acute because of the perception that TC-ASD was technically straightforward and demonstrably

safer than O-ASD, the catastrophic potential of erosions, and the fact that erosions appeared to occur unpredictably and as much as years after device implantation. Rapidly, a board of physicians was convened to review known cases of device erosion, identifying deficient anterior-superior or retro-aortic rim (along with device over-sizing) was identified as a risk factor present in all of their cases [19]. In 2012, a United States Food and Drug Administration Panel Review convened and was followed by revision of the manufacturers Indication for Use, labeling a retro-aortic rim <5mm in diameter as a relative contraindication to TC-ASD with an ASO device[20–22]. Concern for device erosion has persisted [23–27], but limitations in longitudinal follow-up of implanted devices has made it impossible to accurately measure the number of devices implanted, the total number of erosions, and the risk of erosion. Best estimates of risk are between 0.04 and 0.3% of device implants[19,21,23,24,28]. Most cases of erosion occur shortly after device implantation, but erosions have been reported as late as 8 years after initial placement[29,30].

The low overall rates of erosion and limited experience at individual centers has complicated identification of patient- and procedure-level risk factors for device erosion. Neither the first version of the IMPACT® [9] nor C3PO [10] contained data about post-discharge adverse events. Since that time, a prospective post-market surveillance study of the ASO was initiated. However, enrollment was stopped in December of 2016, and the results have yet to be published. In the first revision of the IMPACT® registry the capacity to include follow-up data for pre-specified interventions including TC-ASD was added. It remains to be seen whether centers are accurately reporting their longitudinal data in this voluntary database. Without manufacturer or registry follow-up, use of other large (non-clinical) observational data-sets (e.g. insurance claims data) may be necessary to obtain better estimates of erosion risk in the current era.

At present, it remains up to individual cardiologists to determine whether TC-ASD is the best option for ASD closure. There is not, as of yet, data to determine whether 1) anatomic variations (bare vs. small retro-aortic rim or concomitant deficient superior tissue rim) or 2) a combination of anatomy and choice of device (a patient with deficient retro-aortic or superior rim and a large or over-sized device) can provide predict superior risk stratification[19,28,31]. Though deficient retro-aortic rim has consistently been found in erosion cases, it is not sufficient to identify which patients are at risk for erosion. Subsequent research has demonstrated that the prevalence of deficient retro-aortic rim is between 40–60% of children referred for TC-ASD[8,9,32,33] and slightly lower in adult patients[34]. A recent case-control study using data from the Erosion Board's collection and the ASO Post-Approval Study reiterated 1) that deficient retro-aortic and superior vena cava rims were present in a much higher proportion of cases than controls, 2) ASD were larger in diameter and larger in proportion to patient weight than in controls, and 3) several factors suggestive of device over-sizing (balloon size much larger than static defect size or device much larger than static defect size) were more common in cases and controls[28]. Operators are now cautious not to allow devices to indent the retroaorta or roof of the left atrium, but debate remains about “splaying” the ASO device around the aorta as shown in Figure 2. There continues to be more work to identify the factors or combination of factors that identify patients in which the risk of TC-ASD exceeds that of O-ASD.

It is important to reiterate that the relative clinical benefit of TC-ASD to O-ASD is well established. In head to head comparisons, TC-ASD has consistently demonstrated equivalent efficacy with excellent safety in comparison to O-ASD[4,35,36] with the added benefit of having significantly less discomfort, superior cosmetic results, and a shorter length of stay. Reevaluating these outcomes outside of clinical trials is challenging. There are relatively few contemporary series comparing the results of TC-ASD and O-ASD. Large multicenter series are necessary for comparisons because of systematic differences between patients undergoing O-ASD and TC-ASD and the need for statistical adjustment to account for confounding by indication. Contemporary multi-center series of TC-ASD have demonstrated the risk of in-hospital mortality is 0–0.015% [9,10,37]. In the same time period, data from the Society for Thoracic Surgeons Congenital Heart Surgeons database suggests that the risk of in-hospital mortality after O-ASD is between 0.3–0.9% even after adjusting for pre-operative risk factors[38]. Even adjusting for measurable differences in case-mix, studies have consistently demonstrated that peri-procedural morbidity (i.e. complications) is significantly higher after O-ASD as well[39], which is also reflected in a longer length of stay and higher hospital costs following O-ASD[39,40]. Even with uncertainty regarding what the risk of “real” current risk of erosion is (which is likely a function of both patient selection and device selection), the additional risk of erosion is unlikely to overcome the relative benefits of TC-ASD over O-ASD.

However, in light of this concern it is important to determine whether concern regarding erosion is affecting practice. Analysis of clinical registry data demonstrated that patients with deficient retro-aortic rim were no less likely to receive ASO devices than those with larger retro-aortic rims[9]. At the same time, analysis of administrative data has allowed, for the first time, measurement of the tendency to pursue O-ASD and TC-ASD[9], demonstrating that prior to 2013, the proportion of TC-ASD was increasing, but that between 2013 and 2015 this trend reversed and the proportion of O-ASD increased slightly relative to TC-ASD (Figure 4). Though this trend may reflect the reasonable desire to avoid erosions, this trend in practice would potentially have risks. Though referring patients for O-ASD will inevitably reduce the risk for erosion, this practice only results in a net reduction in harm to patients if the benefit exceeds the inherently higher risks of O-ASD.

Another trend seen in this data is a trend towards closing ASD in progressively younger patients. From the outset of TC-ASD, smaller children have had ASD closed. In the ASO device trial, there was no restriction on age or size for the TC-ASD arm, and the median age of subjects was 9.8 years with a range from 0.6 to 82 years[4]. Similarly, the first multicenter study reporting real-world use of the ASO device, reporting the results of 478 cases from 13 centers performed between 2004 and 2007 demonstrated an equally broad range (infancy to the ninth decade of life)[5]. In that series, 33% of reported cases were performed in patients <16 kg. Since that report, multiple case series demonstrate that TC-ASD can be performed even in patients <10 kg[32,41–45]. At the same time, the majority of cases continue to be performed in school-age patients. Contemporary data from the IMPACT® registry that the median age of TC-ASD is 5–7 years[9,37] with a similar series from the C3PO registry reporting that 85% of subjects were older than 3 years[10].

Though natural history studies of large ASD demonstrated a decrease in life expectancy, childhood symptoms due to congestive heart failure were rare as was the development of pulmonary vascular disease [46–48]. Other series have demonstrated that the majority of small defects found in infants close spontaneously [49–51]. The natural history of larger defects has not been well defined. In cross-sectional analyses, an association has been demonstrated between older patient age at diagnosis and larger defect size [50,51]. This may be due to spontaneous closure of smaller defects, but some have hypothesized that some ASD increase in size over time [52]. This has been used as a justification for early intervention. No studies have followed ASD longitudinally to confirm if some ASD do grow over time. Even if some ASD did grow, it is unclear whether how often that growth would complicate TC-ASD.

Analysis of data from the PHIS registry demonstrated that the age of patients undergoing ASD closure at primary pediatric hospitals in the US decreased progressively between 2007 and 2015 [9], independent of measurable patient-level confounders. It is impossible to determine in this study design the reasons behind this trend. Sensitivity analyses demonstrated that this was not driven by the aforementioned trend to increasing use of O-ASD and was present regardless of closure method. There is also no evidence that the trend is the result of increasing prevalence of pulmonary disease or prematurity that might aggravate the physiological effects of an atrial level shunt. This trend has the potential to have real ramifications on patient safety. The effect of small size on the risk of adverse events or technical failure has been equivocal in multiple studies [8–10]. However, McElhinney and colleagues demonstrated that larger defect size to patient size was a risk factor for device erosion [28]. Therefore, for TC-ASD, the optimal age for closure is not clear, and it remains the shared responsibility of referring physicians and interventional cardiologists to balance these risks and benefits.

These studies have demonstrated that there is more uncertainty regarding which patients should be referred for TC-ASD than what one might have expected. This is underscored, by variation in the relative utilization of TC-ASD and O-ASD, even at relatively large primary pediatric hospitals. Though TC-ASD accounted for >80% of ASD closure procedures at US pediatric hospitals [9], some hospitals utilized TC-ASD for as few as 30% of their ASD closure cases, while others were as high as 100% [9]. Even after adjusting for differences in case-mix, there remained significant inter-hospital variability in the choice between O-ASD and TC-ASD [9]. The systematic differences between hospitals underscores the lack of consensus about how ASD should be treated. Similar differences between hospitals have been seen in both the distribution of indications for TC-ASD and how different hospitals define right ventricular volume overload [53]. Taken together, these observations demonstrate the lack of consensus in practice for TC-ASD and the potential benefit of standardization of practice.

Minimally invasive cardiac surgery:

In considering the potential risk of device erosion, an important question is whether O-ASD can be made safer and less morbid for patients. Minimally invasive cardiac surgery (MICS), through “mini-sternotomy” or video assisted thoracoscopic surgery (VATS) (with or without

robotic assistance), has the potential to reduce procedural morbidity relative to open heart surgery with reductions in length of stay along with improved cosmesis compared to conventional surgical correction of ASD[54]. However, to date the largest case series of MICS report lengths of stay (median between 5–7 days) that are similar to conventional studies and much longer than that following TC-ASD (1 day or less) [55–58]. Enthusiasm and expertise in MICS remains limited to a few centers and is not yet a compelling alternative to conventional O-ASD and TC-ASD.

PFO closure as secondary prophylaxis for stroke:

The incidence of cryptogenic stroke in young adults is between 15 and 35%[59]. A possible mechanism for these strokes is transient right to left shunt through a patent foramen ovale allowing embolization of thrombus from the systemic venous circulation into the systemic arterial circulation (and eventually the brain). As a result, there has been significant interest in evaluating the relative benefit of device closure of PFO as secondary prophylaxis after a stroke. Three randomized clinical trials (RCT) from 2012–2013 using the Amplatzer PFO occluder (St. Jude Medical, St. Paul MN) [60,61] and the STARFlex closure system (NMT Medical, Boston MA)[62] failed to demonstrate benefit over medical therapy. Therefore 2016 American Academy of Neurology recommendations stated that there was insufficient evidence to endorse device closure of PFO after cryptogenic stroke[63]. However, two recent RCT have demonstrated a significant benefit of TC-PFO over medical therapy: the REDUCE[64] and CLOSE [65] trials. The two more recent studies differed from prior studies in that they restricted enrollment to patients in whom a right to left shunt could be elicited on bubble-study echocardiogram. A number of meta-analyses have been applied to these data, pooling data from previous trials. The most recent of these[66] demonstrated that the benefit of device closure was greater in patients with larger right to left shunt (i.e. a larger number of microbubbles) on agitated saline contrast echocardiogram and in the subgroup of patients <45 years. The pooled benefit over medical therapy was still relatively modest (number needed to treat between 28 and 64 to prevent one stroke over 4 years depending on which estimate of stroke recurrence risk was used), but supported the benefit of TC-PFO over medical therapy[66]. Concerns over the increase in risk of atrial fibrillation with TC-PFO appear to be largely driven by events in cases in which the STARFlex system was used and there was no significant difference in major adverse events between TC-PFO and medical therapy groups in this meta-analysis[66]. Additionally, reanalysis of the RESPECT trial data after longer follow up time (median: 5.9 years, compared to previously published data after a median of 2.1 years) demonstrated significant benefit to TC-PFO over medical therapy consistent with REDUCE and CLOSE, and demonstrating increased benefit in larger shunts on agitated saline injection [67].

At the present time, both the Amplatzer PFO occluder and the Gore Cardioform device are approved by the United States Food and Drug Administration for the closure of PFO as secondary prophylaxis for stroke. As these results disseminate, it is likely that pediatric/congenital cardiologists will be asked to be involved in PFO closure in both adults and in children. At the present time, several questions are important to consider when translating the data from clinical trials and meta-analyses to clinical practice. First, the definition of cryptogenic stroke differs between studies and needs to be clarified both to provide an

accurate measurement of recurrence risk and to determine patients in whom TC-PFO closure is less likely to be effective. Second, in light of relatively modest benefits in absolute risk reduction, it is important to determine what factors (in addition to relatively young age and larger shunt) identify populations that would benefit more from TC-PFO. Third, as with any new application of a technique there is the potential for new or unexpected adverse events along with the anticipated benefits. As an example, several studies have shown that a small but significant minority of patients with ASD and PFO devices develop aortic insufficiency after device closure[68–71]. Addressing all of these issues will require continued vigilance and ongoing clinical effectiveness research as PFO closure becomes more widespread.

Another important issue for pediatric/congenital cardiologists is the applicability of these findings to the pediatric population. The incidence of arterial stroke is lower in children than in older patients, but the proportion of cryptogenic strokes is similar to that in adults, between 15 and 27%[72–74]. It is tempting to extrapolate data from clinical trials in older populations since the benefit TC-PFO are greater robust in younger (i.e. <45 years) adults[66,75], and because children and adolescents will presumably spend more time at risk than even young adults. Documented issues with maintaining patients on chronic antiplatelet or anticoagulant regimens are likely to be even more challenging in the pediatric population. However, at this time there is still a dearth of data in children and it is not a given that recurrence risk for cryptogenic stroke will be similar between pediatric and adult populations. In addition, to the cryptogenic stroke population an open question is whether patients long-term central venous lines or transvenous pacing leads should be screened for PFO and which of these patients should have their PFO treated.

Also, transient ischemic attacks (TIA) are a potentially problematic indication for TC-PFO. TIA are not only much more frequent than cerebrovascular accidents, but also are more problematic from a diagnostic perspective, since they are not always accompanied by findings on neuro-imaging studies and have overlap in symptoms with migraines and other conditions. Diagnosis of TIA in a pediatric population is also more challenging due to the cognitive development of the population. Further research is necessary to clarify these issues and until that time, there is uncertainty in regards to what the appropriate care of these children should be.

Non-implant defect closure:

While most closure techniques for atrial septal defects and PFO's rely on implantation of a permanent device within the defect such as an Amplatzer device or Cardioform device, the ideal closure device would not utilize a foreign body. This "ideal" ASD closure device would obviate the need for concern over thrombus formation, embolization, erosion, arrhythmias, and the ability to access the left atrium later in life. Clearly, with the increase in interventions for atrial fibrillation, mitral valve dysfunction and left atrial appendage occlusion, transcatheter access to the left atrium is valuable and permanent implants in the atrial septum can make this much more difficult. Although the initial "non-device" closure techniques have been used predominantly for closure of PFOs (patent foramen ovale), it is important to consider these creative techniques as similar technology could someday be utilized for ASD closures.

The initial concept for non-device closure of ASDs utilized radiofrequency (RF) energy to essentially “weld” together the tissue flaps or tunne l which created a PFO. By applying RF energy to heat tissue flaps while pushing them together or utilizing a vacuum to keep the septum primum and secundum opposed to one another, the injury and heat created from the RF energy allows the tissue to become adherent and then to heal together. The pathology of radiofrequency closure of PFOs in animals has been described and reported in a porcine model[76] and the first human implant was performed in 2005[77]. This is marketed as the RFX closure system (Cierra Inc, Redwood City, CA). In a study of 144 patients lead by Dr. Horst Sievert, the RFX device was found to be safe as there were no significant adverse events in any of the patients except one patient who received a blood transfusion for blood loss during the procedure. However, at 6 month follow up 45% of the PFOs continued to have a significant shunt. The device was much more effective (72% closure at 6 months) in closing smaller PFOs with stretch diameters less than 8 mm[78].

Another new device that is being used in Europe and now also in North America is the NobleStitch Device made by HeartStitch (Fountain Valley, CA, USA). This device works by passing two sutures through different aspects of the PFO and creating a knot to suture the PFO into a closed position (Figure 5). This device and its accessories are CE marked for cardiovascular suturing and PFO closure in Europe. Although this device is not approved in the United States for PFO closure, it is now being used off label for this procedure. The first reported series of cases with this device were reported in a prospective study from 12 centers in Italy[79]. This study enrolled 192 patients who were considered acceptable candidates for suture-mediated PFO closure. The NobleStitch EL system was technically successfully in 96% of the patients with no procedural or long-term complications reported. At follow up time of about 7 months, contrast echocardiography with Valsalva showed no shunting in 75% but a “significant” shunt was seen in 11% of the patients. Although use of radiofrequency energy may be difficult to translate to and significant ASD, it may be possible in the future to utilize stitch-based device to close small ASD and even larger ASD with transcatheter patch placement in the future. It may also become possible to employ these sort of techniques along with device closure to minimize the risks of either erosion or embolization for high risk ASDs.

CONCLUSION

Transcatheter device closure of defects in the inter-atrial septum have been performed for over forty years and have demonstrated excellent safety and efficacy. The controversy surrounding the risk of device erosion has brought to light the lack of consensus between different centers how to approach this lesion. Continued innovation in development of devices and epidemiologic surveillance of practice are necessary to provide the best care for patients with ASD.

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KEY POINTS:

1. Transcatheter device closure of ostium secundum atrial defects (ASD) has a lower risk of mortality and morbidity, shorter length of stay, and lower cost than operative closure of the same defect.
2. Erosion of devices after transcatheter closure of ASD remain an important consideration in transcatheter closure of ASD. The best data to date indicates that patients with erosion were more likely than controls to have smaller superior rims, larger defects relative to the septum and patient size, and were more likely to have an oversized device. Though these findings suggest steps that might improve outcomes, further research is necessary to determine whether a specific subset of patients can be identified whose risk of device erosion exceeds the risks of open-heart surgery.
3. Transcatheter ASD closure remains the predominant method of ASD closure in children and young adults, but in recent years (coincident with concern for device erosion) there is a significant trend towards increasing referral for operative ASD closure. Simultaneously, the patient population referred for ASD closure is progressively younger with time. The effect of these trends on outcomes is not clear at this time, but deserves attention.
4. Recent data has demonstrated the benefit of device closure of patent foramen ovale as secondary prophylaxis for strokes in older adults. There is a dearth of data regarding the relative risks and benefits of this practice in younger patients with cryptogenic stroke and PFO. Given the high prevalence of PFO and increasing incidence of stroke in medically complicated pediatric patients, closure of PFO for this indication is likely to be an increasingly important issue for pediatric/congenital cardiologists.
5. A potential innovation in closure of ASD and PFO are approaches that avoid implantation of a permanent device. An example are catheter delivered sutures to close atrial defects such as the NobleStitch device.

Figure 1: Radiographic Appearance of Devices for transcatheter closure of ASD

Digital acquisition images of A) Amplatzer septal occluder (anterior posterior and lateral projections), (Courtesy of Abbott, Inc., Abbott Park, IL; with permission.) B) Gore Cardioform device (en face and orthogonal views), C) Cardioform Atrial Septal Defect Occluder (en face and orthogonal views). (Courtesy of W.L. Gore and Associates, Flagstaff, AZ; with permission.)

Figure 2: Amplatzer Septal Occlusion Device

A) Amplatzer septal occluder (artist rendition – courtesy of Abbott), B) Echocardiographic appearance of the Amplatzer ASD device splayed around the aorta.), (Courtesy of Abbott, Inc., Abbott Park, IL; with permission.)

Figure 3: Gore Cardioform ASD Device

A) Picture of the Gore Cardioform ASD Device, B) Cartoon depiction of the Gore Cardioform Device in situ. (Courtesy of W.L. Gore and Associates, Flagstaff, AZ; with permission.)

Figure 4: Estimated probability of TC-ASD vs. O-ASD 2007–2015

Probability of operative ASD closure versus transcatheter ASD closure

Conditional standardization was used to calculate an adjusted probability of operative ASD closure vs. transcatheter device closure, for a hypothetical white male six-year-old boy with no co-morbid conditions (maroon line with 95% CI represented by the dashed grey lines).

This was based on the mixed effects multivariate generalized linear model summarized in Table 2. The probability of operative ASD closure decreased significantly from 2007 until 2012 (OR: 0.95 per year, $p=0.02$). In 2013, there was a significant shift in probability favoring ASD (OR: 1.21 per year, $p=0.006$).

(From O'Byrne et al 2017 *Increasing Propensity to Pursue Operative Closure of Atrial Septal Defects Following Changes in the Instructions for Use of the Amplatzer Septal Occluder Device*

An Observational Study Using Data from the Pediatric Health Information Systems Database. Am Heart J, 192: 85–97; with permission.)

Figure 5: NobleStitch EI Device for PFO closure

Left) The NobleStitch EI device, Right) Drawing of mechanism of action of the device demonstrating mechanism of action of stitch placement. (Courtesy of HeartStitch (Fountain Valley, CA; with permission.)