

# MedTech STRATEGIST

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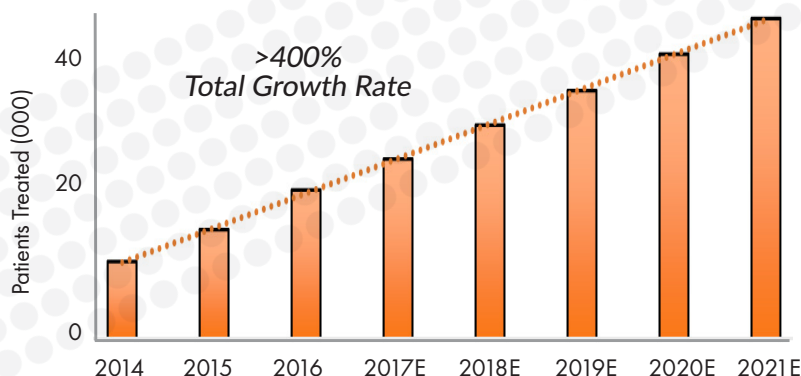
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# Neurovascular Device Market POISED FOR GROWTH

*Next-generation mechanical thrombectomy devices will be the chief driver of growth in the neurovascular device market. New clinical data suggesting that interventional treatment even up to 24 hours after stroke onset is beneficial for some patients could almost triple the number of patients eligible for treatment.*



by  
ODED BEN-JOSEPH, PHD,  
AND SETH BENSUSSEN

## KEY POINTS

■ Not long ago, tPA was the only front-line treatment for acute ischemic stroke. But a second generation of mechanical thrombectomy devices, including stent retrievers and aspiration-based reperfusion devices, has demonstrated significant efficacy against ischemic stroke, providing the impetus for renewed device innovation and new care delivery strategies.

■ This successful new product category has prompted the entry of a new strategic into the field and next-generation competition from a few start-ups, while others are focused on delivery strategies designed to speed up the action of tPA.

■ In the hemorrhagic stroke arena, the embolic coiling market has reached maturity, but flow-diversion devices present a unique, coil-free method for treating complex aneurysms. Early clinical data suggests similar, if not superior, efficacy to stent-assisted coiling.

■ Companies developing next-generation devices could serve as acquisition targets for strategics looking for innovation.

The global neurovascular device market was estimated at \$1.62 billion in 2015 with projected growth to \$2.92 billion by 2024 (see Figure 1). Neurovascular devices broadly cover endovascular treatments for stroke, which is the second leading cause of death globally and the fifth leading cause of death in the United States. Each year, 33 million people worldwide suffer a stroke. In the United States alone, there are roughly 800,000 instances of stroke per year, and this number is expected to increase to one million annually by 2021. Furthermore, stroke is the leading cause of long-term disability in the United States, with related care costs estimated at \$70 billion annually, growing to \$184 billion by 2020. Currently, the neurovascular market is in the middle of a growth phase due to new innovative devices backed by promising clinical data, which has led to successful treatment of new indications, increased adoption in the clinic, and more patients eligible for treatment.

Notable segment activity commenced in the mid-2000s, beginning with **Terumo Corp.**'s acquisition of MicroVention in 2006. Covidien, **Johnson & Johnson**, and **Stryker Corp.** subsequently strengthened their positions in 2010 with the acquisitions of Ev3, Micrus Endovascular, and Boston Scientific Corp.'s neurovascular division, respectively. In

2014, **Medtronic plc** acquired Covidien in a \$42 billion transaction that included all of Covidien's neurovascular products. This was capped with the IPO of neurovascular pure play **Penumbra Inc.** in 2015, for a total of five strategic players in the US market. Stryker currently has the largest market share overall (including both the ischemic and hemorrhagic segments), with 35% of the total market, followed by J&J and Medtronic.

## Coiling Market Strong, But Stagnant

Embolization of intracranial hemorrhages and cerebral aneurysms has been the main focus of the neurovascular field for the past 25 years (see *Figure 2*). Roughly 3% of adults have at least one unruptured aneurysm. Embolic coiling is the established gold standard for treating cerebral aneurysms, backed by strong clinical data (ISAT trial) clearly demonstrating the superiority of embolic coiling over surgical clipping. Furthermore, embolic coiling is cheaper than surgical clipping. With all key players selling their own coiling products and few new companies developing new coils, there is little excitement around new coiling products and any further innovation will likely come from in-house R&D efforts by the strategics. This is evidenced by J&J's recent release of the new *Galaxy G3* mini coils to complement the company's existing coiling line. Small innovation will be made to improve patient outcomes, but overall sales will likely not spike in response to new products. Coiling is the most established and successful product line in the neurovascular field and sales will remain high, but given the already high efficacy, there is little room for market growth (see *Figure 3*).

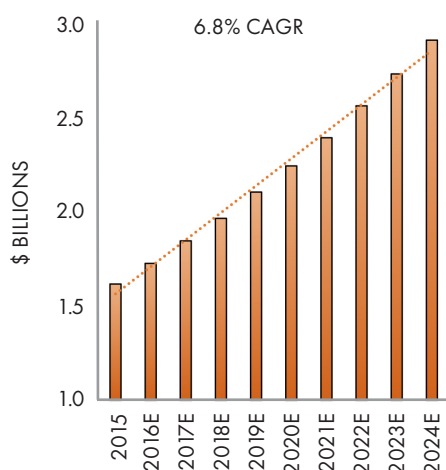
## New Devices Improve Treatment of Complex Aneurysms

Aneurysms with complex morphologies, including large, giant, or wide-neck aneurysms, are difficult to treat with coiling alone. The development of embolization-enabling stents has extended the use of embolic coiling to these complex aneurysms. The placement of the stent helps hold the coil in place for proper embolization of the aneurysm. All key players in the field have embolization-enabling stents marketed under the US Food and Drug Administra-

tion's (FDA) Humanitarian Device Exemption (HDE) designation to treat large, giant, or wide-neck aneurysms. Embolization-enabling stents aid in bridging aneurysm necks, but not all stents are effective in treating all complex morphologies. Clinical studies have experimented with "kissing" and "y-stenting" techniques to use these stents for fusiform or bifurcating aneurysms, but adoption of these techniques is far from widespread. Strategics have looked to smaller start-ups for more innovative ways to address wide-neck bifurcation aneurysms with specific bifurcation stents, as evidenced by J&J's recent acquisition of Pulsar Therapeutics and Medtronic's acquisition and development of the Barrel bifurcation stent. One of the main advantages of bifurcation stents, as opposed to flow-diversion stents, is that bifurcation stents will not impede flow to either of the daughter vessels, while flow-diversion stents will occlude blood flow to one of the daughter vessels (see image at <https://mint.weill.cornell.edu/new-technologies/advancing-vascular-therapies/cerebral-aneurysm-device>). Wide-neck bifurcation bridging will continue to grow, as it increases the number of patients that can be treated safely and effectively by coiling. Yet, it must be noted that this growth will be limited by its utility to only treat complex aneurysm morphologies.

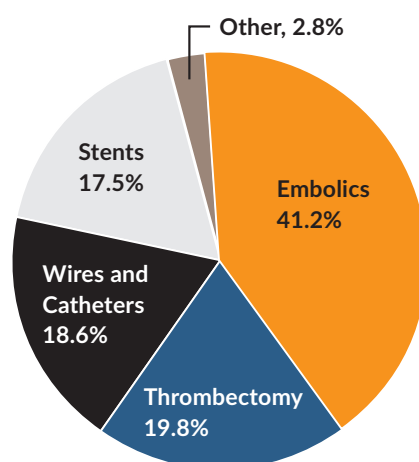
In addition, flow-diversion devices are currently used to treat complex aneurysms that cannot be treated by coiling alone. One key difference is that flow-diversion devices act as stand-alone devices and no coiling is necessary for

**Figure 1**  
**Global Neurovascular Market 2015-2024**



Source: Outcome Capital

**Figure 2**  
**Neurovascular Market Stratification**

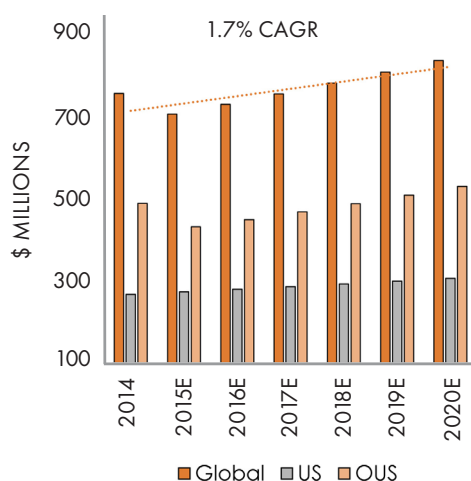


aneurysm occlusion. There are currently two types of flow-diversion devices: flow-diversion stents and intrasaccular devices, comprising a market that is growing at about 12% annually (see Figure 4). Similar to embolization-enabling stents, flow-diversion stents exhibit an increased surface area, which directs a higher volume of blood away from the aneurysm and makes coiling unnecessary. Eventual thrombosis of the aneurysm and endothelialization occurs. One advantage is that the device never has to enter the

aneurysm, which is more unstable than the parent vessel. Flow-diversion stents can also be coupled with coiling as a way to treat both the aneurysm sac and the vessel. Flow-diversion stents are a favorable method for treating large or giant aneurysms in the internal carotid artery, presenting few complications and high occlusion rates (<https://jamanetwork.com/journals/jamaneurology/fullarticle/2527561>), but further data is needed on long term occlusion given the novelty of these devices. Medtronic,

Figure 3

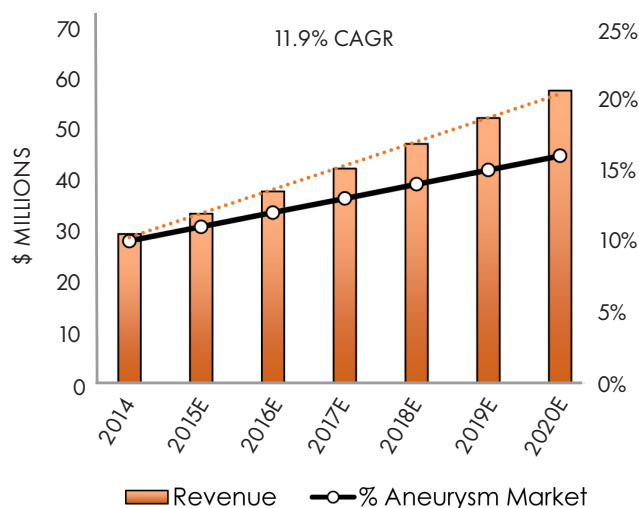
### Projected Global Coils Market 2014-2020



Source: Outcome Capital

Figure 4

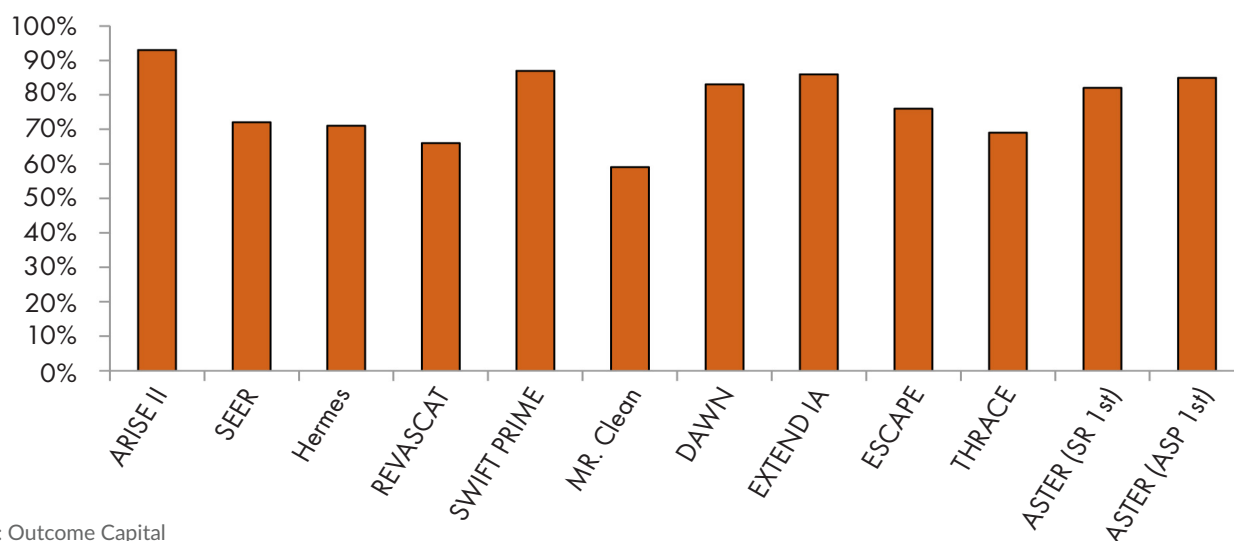
### Projected US Flow Diversion Market 2014-2020



Source: Outcome Capital

Figure 5

### mTICI 2b-3 Reperfusion



Source: Outcome Capital

Stryker, and Terumo all have flow-diversion stents as well as several other smaller companies. Medtronic's *Pipeline* and *Pipeline Flex* devices are the only FDA approved flow-diversion stents, with Terumo's *FRED* beginning FDA trials. Currently, flow-diversion stents are only used to treat unruptured aneurysms due to their common pairing with dual antiplatelet therapy, but the *Pipeline Flex* with *Shield* technology is in trials for ruptured aneurysms. As noted above, flow-diversion stents are not ideal for treating bifurcation aneurysms because they decrease blood flow to one of the daughter vessels.

In contrast to flow-diversion stents, intrasaccular devices are deployed inside the aneurysm neck or sac depending on the device. Similar to flow diversion stents, intrasaccular devices are generally made from a tight woven mesh to disrupt blood flow into the aneurysm sac and help promote thrombosis inside the aneurysm. These devices remain in place by exerting radial force on the aneurysm neck. Intrasaccular devices are suitable for treating all types of aneurysms, including wide-neck bifurcation aneurysms, because they are restricted to the aneurysm neck and thus will not occlude daughter vessels. In addition, these devices do not require dual antiplatelet therapy, so they are suitable for treating both ruptured and unruptured aneurysms. Early clinical results suggest superiority of intrasaccular devices over stent-assisted coiling. A meta-analysis of 588 cases treated with Terumo's *WEB* intrasaccular device showed an 85% occlusion rate after seven months, compared to a 73% occlusion rate with stent-assisted coiling (<http://evtoday.com/2017/02/endovascular-advances-in-the-treatment-of-cerebral-aneurysms/>). Medtronic and Terumo are currently the only strategies with intrasaccular devices, with Medtronic recruiting for trials and Terumo's *WEB* undergoing clinical trials, but there are a few start-up companies developing these devices that could be prime acquisition targets for the rest of the field.

Many key players in the field are focused on effective treatment of complex aneurysms. There currently is not one standard approach but, rather, several approaches, each with its advantages and disadvan-

tages. J&J has focused on the stenting approach with its acquisition of Pulsar Vascular, while Medtronic is hedging its bets with the Barrel bifurcation stent as well as intrasaccular devices acquired from **Medina Medical** and **Nfocus Neuromedical**. In addition, Terumo's *WEB* intrasaccular device, acquired in the Sequent Medical transaction, and *FRED* flow-diversion device are both currently undergoing FDA trials. Other smaller companies are developing new flow-diversion stents, bifurcation stents, and intrasaccular devices, which could lead to more deals in this area.

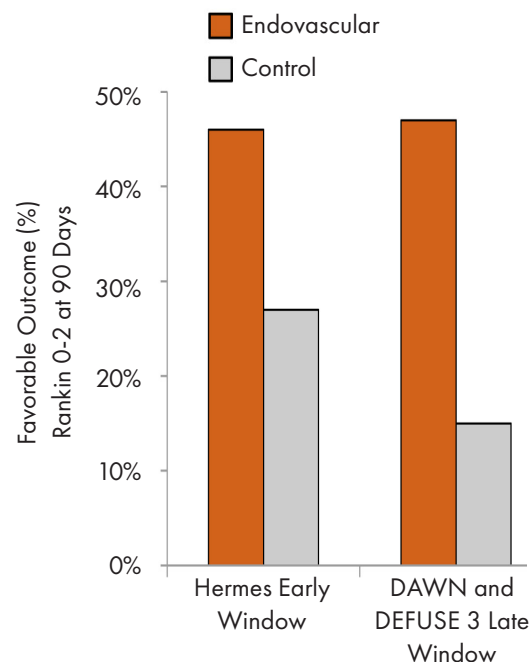
## Innovative New Devices: Positive Clinical Data Drive Ischemic Stroke Market Growth

Effective treatment of acute ischemic stroke has remained elusive until recently, despite the fact that 87% of all strokes are ischemic in nature. Chemical thrombolysis using tissue plasminogen activator (tPA) has been the standard treatment for ischemic stroke until mechanical thrombectomy was approved as a first line therapy in 2016. The *Merici Retriever*, developed in 2004, was the first mechanical thrombectomy device, but it demonstrated very modest results. As recently as 2012, the SYNTHESIS and MR RESCUE trials did not show favorable outcomes for mechanical thrombectomy compared to tPA alone. It wasn't until second-generation devices became available—including Medtronic's *Solitaire* and Stryker's *Trevo* stent retrievers and Penumbra's aspiration system—that me-

chanical thrombectomy truly became a viable treatment option. In addition to better device designs, trials employing these new devices also limited treatment to patients with large-vessel occlusions and utilized advanced imaging technology to assist in patient selection. Data from five landmark clinical trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND IA), first released in late 2014, demonstrated statistically significant improvement in patient outcome using these new mechanical thrombectomy devices coupled with tPA administration, compared with tPA alone, and essentially launched a new era in ischemic stroke treatment. (See "Recent Trials Hint at Bright Future for Ischemic Stroke Devices," MedTech Strategist, December 18, 2014; *Launching a New Era in Ischemic Stroke Intervention: A*

Figure 6

### Late Window Paradox



Source: Outcome Capital



*Conversation with Medtronic's Brett Wall," MedTech Strategist, July 20, 2015; and "Device Market for Ischemic Stroke Gains Momentum," MedTech Strategist, July 5, 2017.)*

**These studies strongly suggest that an imaging-based approach is better than a time-based approach for determining whether patients are eligible for intervention.**

Following publication of these five trials, the American Heart Association (AHA) issued a Class 1 level of evidence for endovascular therapy for treating acute ischemic stroke with stent retrievers approved for use six hours after stroke onset and aspiration devices approved for use eight hours after stroke onset (see Figure 5).

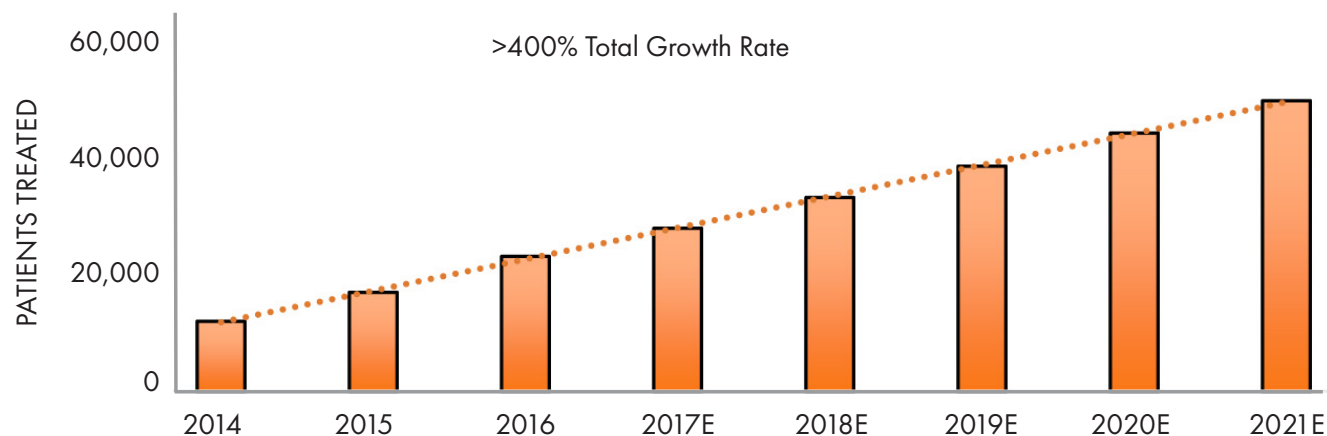
While these next-generation thrombectomy devices allow for the successful removal of large vessel occlusions, time to treatment remains the biggest barrier in effectively treating stroke. It has been said that "time is brain" in reference to the fact that almost two million neurons die per minute of ischemic stroke—the equivalent of the brain aging about 3.5 years every hour without treatment (<https://www.ncbi.nlm.nih.gov/pubmed/16339467>). To prevent long-term disability, ischemic strokes must be diagnosed and treated as quickly as possible. Currently, only 18.6% of eli-

gible patients are actually treated for ischemic stroke and many are denied treatment because they arrive at the hospital too late or they are taken to a facility that is not certified to offer endovascular treatment. However, the time restriction has eased considerably with the recent release of additional data suggesting that endovascular treatment can benefit many more patients, including those who present up to 24-hours following stroke onset or those who wake up with a stroke of unknown onset. The recently completed DAWN and DEFUSE 3 trials investigated the use of mechanical thrombectomy to treat ischemic strokes in late-presenting patients (from six hours to up to 24 hours after onset) who were selected based on imaging studies that analyzed their volume of salvageable brain tissue. These studies strongly suggest that an imaging-based approach is better than a time-based approach for determining whether patients are eligible for intervention (see Figure 6). Both trials showed strong results, leading the AHA to issue revised clinical guidelines earlier this year, recommending mechanical thrombectomy treatment in carefully selected large-vessel ischemic stroke patients up to 24 hours since last known normal. (See "Technologies to Watch in 2018: New Data and More Expansive Guidelines Give Ischemic Stroke Market a Push," MedTech Strategist, April 20, 2018.)

These new guidelines allow patients suffering from "wake-up strokes" to still be eligible for treatment, and they increase the overall potential patient population by 270%. In February, Stryker, which sponsored the DAWN trial, was granted an expanded label by FDA for its *Trevo* stent retriever, which is now approved as a first-line therapy for selected patients who present within 24-hours of stroke onset.

Figure 7

### Projected Ischemic Stroke Patients Treated in the US 2014-2021



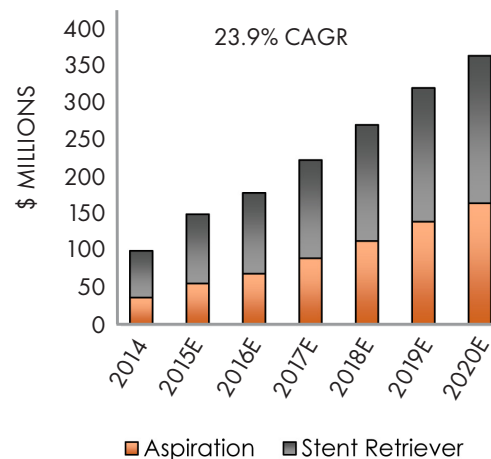
Source: Outcome Capital

Given the strong clinical data demonstrating the efficacy of mechanical thrombectomy and the recent extension of the time window for treatment, there is strong competition among strategics and other smaller companies to develop innovative, next-generation devices for ischemic stroke. Medtronic, Stryker, and Penumbra are currently the only players in the US market. All three are working to expand their ischemic stroke device portfolios. Penumbra, which demonstrated in the COMPASS trial that its aspiration system is noninferior to stent retrievers as a first-line therapy, has received FDA approval of its 3D revascularization device (stent retriever) to complement its *ACE* aspiration device. Moreover, the FDA recently cleared ischemic stroke aspiration systems from both Medtronic and Stryker. In addition, there are several other companies with stent retrievers marketed in Europe or still under early-stage development. There is clearly interest from the other strategics, including J&J, which purchased Neuravi (and its next-generation *EmboTrap II* stent retriever), and Terumo, which is developing its own next-generation device (*ERIC*). J&J's purchase of Neuravi in 2017 was "the largest deal for a venture-backed medtech company in Europe since Medtronic's \$700 million buyout of CoreValve in 2009." Results from the ARISE II trial using the *EmboTrap II* device demonstrate its efficacy and possible improvement on existing stent retrievers and the *EmboTrap* was FDA cleared this month. The *Trevo* and *Solitaire* devices were groundbreaking and opened the doors for treating ischemic stroke, and now the next generation of devices will continue this growth through improved treatment speed and increased efficacy.

As mentioned, the strong clinical data from these devices led to updated guidelines by the AHA for using mechanical thrombectomy to treat stroke, but many patients are still not transported by first responders directly to hospitals that are able to perform these procedures. Moreover, in certain areas of the country, facilities with the highest level of stroke treatment certification—known as comprehensive stroke centers—may be few and far between. To ease that treatment bottleneck, in January the AHA/ASA added a new certification program for "thrombectomy-capable stroke centers," designed to identify hospitals that are "well equipped" to treat patients with large-vessel strokes—including meet-

Figure 8

### Projected US Mechanical Thrombectomy Market 2014-2020



Source: Outcome Capital

ing rigorous standards for performing mechanical endovascular thrombectomy—but that may be bypassed by first responders because they fall short of being classified as a comprehensive stroke center. Although comprehensive stroke centers remain the preferred place for stroke treatment, this new designation allows more patients to receive endovascular thrombectomy within the approved time window.

Meanwhile, studies such as RACECAT (Medtronic) are looking into how inter-hospital transfers affect patient outcomes, and new imaging devices are being developed to more effectively and quickly diagnose stroke. Early studies are investigating the use of mobile stroke units to diagnose stroke as early as possible and ensure patients are directed to hospitals where thrombectomy is

performed. These new mechanical thrombectomy devices have made it possible to effectively treat ischemic stroke, and now the field is adapting to enable patients to receive proper treatment. With new guidelines and diagnostics, more patients will become eligible for treatment and that will continue to drive growth in this market (see Figures 7 and 8).

## Conclusions

While mechanical thrombectomy is the lead driver of growth in the neurovascular field, the more established aneurysm market is focused on finding effective treatments for wide-neck bifurcation aneurysms. Embolic coiling has been established as the standard of care for most ruptured and unruptured aneurysms, which is the reason it currently accounts for about 70% of the neurovascular market. However, while the market is large, the utility of coiling has been realized and will remain steady with single-digit annual growth. The treatment of complex aneurysms has proven more difficult. Embolization-enabling stents and flow-diversion stents have enabled the treatment of large, giant, or wide-neck aneurysms. Yet, the recent deal history and lack of effective treatments suggest that there is room for improvement for treating wide-neck bifurcation aneurysms. Several companies are developing new bifurcation stents and intrasaccular devices, which could lead to more deals in this area. Whereas embolization-enabling stents will always be limited to complex aneurysm morphologies,

strong clinical data could lead to widespread adoption of flow-diversion stents and intrasaccular devices for treating aneurysms with less complex morphology.

However, mechanical thrombectomy presents the largest growth opportunity in the neurovascular field. New results from the DAWN and DEFUSE 3 trials have expanded the approved treatment time with mechanical thrombectomy devices in selected patients up to 24 hours since last known normal, and the AHA/ASA has added the new thrombectomy-capable stroke center designation enabling more stroke

patients to receive thrombectomy procedures within the approved time window. The number of ischemic stroke patients treated with neurovascular devices is expected to increase over 400%, and the market is expected to grow at a strong 20% compound annual growth rate over the next five years. In addition, several smaller companies are developing the next generation of thrombectomy devices geared toward quicker deployment times, fewer post-surgical complications, and increased efficacy—all leading to improved outcomes for stroke patients.

Overall, the neurovascular market will grow due to the continued development of innovative new devices, which will enable the treatment of more patients and improved clinical outcomes. Although the deal market is relatively slow in the field, the number of transactions has remained fairly consistent over the past five to seven years, with values close to or above \$100 million, making it worthwhile for new companies to continue developing new devices (see Figure 9). There have also been efforts to develop new devices for early detection of stroke and the testing of mobile telestroke units to help diagnose strokes earlier and reduce the amount of time between stroke onset and treatment. This, coupled with increasing the number of trained stroke interventionalists, will also help drive market growth by helping more patients receive proper treatment. Most importantly, current and future neurovascular devices will help save lives, reduce rehabilitation time and return hospital visits, and decrease the long-term disability costs associated with stroke. 🍌

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Figure 9

### Stroke M&A: 2013-2017

Announcement Date	Target	Acquirer	Transaction Value (\$ millions)	Device Type
4/10/2017	Neuravi	Johnson & Johnson (Cadman Neuro)	N/A	Mechanical Thrombectomy
12/8/2016	Pulsar Vascular	DePuy Synthes (Johnson & Johnson)	N/A	Embolization Assist
9/2/2016	Blockade Medical	BALT	N/A	Embolization
7/14/2016	Sequent Medical	Terumo	\$280	Embolization
9/28/2015	Lazarus Effect	Medtronic	\$100	Mechanical Thrombectomy
9/25/2015	BALT Extrusion SA	Bridgepoint Advisers Limited	\$392.18	Neurovascular
8/31/2015	Medina Medical	Medtronic	\$150	Embolization
3/30/2015	TrinTris Medical	Teleflex	N/A	Balloon Catheter
8/22/2014	Reverse Medical	Covidien	N/A	Embolization Assist
6/16/2014	Covidien	Medtronic	\$42,900	Medical Device
7/1/2013	CoAxia	ZOLL Medical	N/A	Balloon Catheter
2/19/2013	Nfocus Neuromedical	Covidien	\$50	Embolization

Source: Outcome Capital