Endovascular Repair of Aortic Disease: A Venture Capital Perspective

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ABSTRACT

Endovascular devices for the treatment of abdominal and thoracic aortic disease are poised to become the next \$1 billion medical device market. A shift from open repair to endovascular repair, advances in technology, screening initiatives, and new indications are driving this growth. Although billion-dollar medical device markets are rare, this field is fraught with risk and uncertainty for startups and their venture capital investors. Technological hurdles, daunting clinical and regulatory timelines, market adoption issues, and entrenched competitors pose significant barriers to successful new venture creation. In fact, the number of aortic endografts that have failed to reach commercialization or have been pulled from the market exceeds the number of Food and Drug Administration–approved endografts in the United States. This article will shed some light on the venture capital mind-set and decision-making paradigm in the context of aortic disease.

KEYWORDS: Venture capital, endovascular therapy, endografts, aortic disease, aneurysms

Objectives: Upon completion of this article, the reader should be able to identify the structure, criteria, and history of venture capital investment in technologies addressing aortic disease.

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VENTURE CAPITAL

Innovation in health care often occurs in small, early stage companies that rely heavily on venture capital financing and support. Venture capital is the link between new ideas and the capital to turn those ideas into marketable products or services, and venture capitalists are intimately involved in the formation and governance of startup companies. Due to the high risk, the uncertainty of outcomes, and the long-term nature of life

sciences commercialization, venture investment is often the only funding option for these small companies.¹ In the medical device industry in 2006, a remarkable 83% of employment is estimated to have stemmed from venture-backed firms.²

Venture capitalists put money into early stage companies in exchange for ownership, or “equity,” in the company. Follow-on investments provide additional capital as the company grows and reaches certain

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milestones (e.g., design freeze, successful animal trials, successful human trials, Food and Drug Administration [FDA] approval, etc.). These “rounds” of financing, often denoted Seed, Series A, Series B, Series C, and so on, typically occur every year or two. Because there is no open market that sets the price of this equity, the valuation at which the venture capital firm purchases shares in each round is a matter of negotiation between the venture capitalist, the company management, and other investors or stockholders. Following an initial investment, it typically takes 3 to 8 years before the firm can “exit” the investment through an acquisition of the company or an initial public offering (IPO). In the interim, the shares in the company have paper value only because there is no market to sell those shares—the investment is “illiquid.” There is little realized value until the company is acquired or goes public. Profitability is often even further away. Venture capital is an extremely high-risk, long-term investment vehicle.

Structure of Venture Capital

Venture capitalists are essentially managers of risk capital. They spend their time raising money, sourcing investment opportunities, performing due diligence on potential investees, pricing and structuring investments, monitoring and adding value to portfolio companies, and seeking ways to exit their mature investments. The venture capital firm is the general partner (GP) of a venture capital fund, and the institutional investors in the fund (or funds) are called the limited partners (LPs).

Venture capital funds are typically organized as fixed life partnerships, usually having a life of 10 years.

A typical financial arrangement between the GP and the LPs is what is termed the “2 and 20” rule, meaning the GP earns an annual management fee of 2% of the committed capital during the period of investments (often less in later years) and 20% of the profits of the fund, also called the “carry.” The carry is the GP’s fee for carrying the management responsibility and all the liability of the fund. For example, if a fund was raised with \$100 million of committed capital, and after 8 years, \$80 million of investments (\$100 million less accumulated management fees) made in the fund returned \$200 million via IPOs and acquisitions, the fund would pay back the original \$100 million investment in the fund to the LPs, distribute an additional 80% of the profits (\$80 million) to the LPs, and distribute 20%, or \$20 million, of the “carried interest” to the GPs. There are many different flavors of this arrangement, but this is the basic structure. Meanwhile, the GP has collected 2% of \$100 million, or \$2 million annually, to manage the fund (pay salaries, office rent, expenses, etc.) (Fig. 1).

Venture Capital and Medical Devices

The venture capital business is by nature high risk, thus the institutional investors (LPs) in venture capital funds expect significant returns for the risk they are taking on when they invest in venture capital funds. The average annual 10- and 20-year returns (after management fees and carried interest) for venture capital funds as of June

Figure 1 Structure of venture capital.

30, 2008 were 16.6% and 16.9%, respectively, as compared with 1.2% and 8.0%, respectively, for the S&P500.³ Yet the number of venture-backed firms that eventually fail is estimated at over 53%.² And not all IPOs or acquisitions necessarily generate high returns. To achieve 15 to 20% returns in the face of company failures and mediocre exits, a subset of investments must have returns much greater than the average. This is the home run philosophy of investing, that is, one home run makes up for lots of strikeouts.

Although medical device-specific venture capital returns are difficult to estimate, the amount of capital invested into medical devices companies was 14%, or \$4.3 billion, of the \$29.9 billion of venture capital invested in total in 2007, and represented 45% of the dollars allocated within the health care sector.⁴ Medical device venture capitalists need to invest in those innovative technologies that can be applied to market opportunities with significant revenue potential to achieve returns well above the costs of development. The estimated cost to successfully develop and commercialize a medical device (often requiring a premarket approval [PMA] clinical trial) is approximately \$40 to \$100 million.⁵ Three of the leading venture-backed aortic endograft companies, TriVascular2, Inc. (Santa Rosa, CA), Aptus Endosystems, Inc. (Sunnyvale, CA), and Nellix Endovascular Inc. (Palo Alto, CA) have each raised \$65, \$59, and \$20 million to date, respectively.⁶ Considering the significant cost of development, well-known medical device venture firms often list investment criteria on their websites that include addressable market opportunities of \$500 million to \$1 billion or greater.⁷

AORTIC DISEASE

Venture Capital and Endovascular Repair of Aortic Disease

Venture capitalists have been involved in the funding of innovative endograft companies since the late 1980s, helping to start early pioneers like Prograft Medical, Inc., AneuRx, Inc., and EndoVascular Technologies Inc., the original manufacturers of the Excluder, AneuRx, and Ancure endografts, respectively. After almost 20 years of market development and clinical trials, endografts are becoming the standard of care for certain aortic disease presentations and have become the most recent medical device product category to knock on the door of the billion-dollar club. There are still unmet clinical needs, and venture capitalists continue to fund innovative endograft companies (Table 1).

The Aortic Endograft Market

Unlike the pharmaceutical and biotech markets, where multibillion-dollar product categories are common (lipid

regulators \$18.4 billion in 2007, proton pump inhibitors \$14.1 billion in 2007), billion-dollar-plus medical device categories are still somewhat rare.⁸ Besides cardiology blockbusters like coronary stents (\$5.2 billion in 2007) and implantable cardioverter-defibrillators (\$5.7 billion in 2007) and orthopedic categories like hips and knees (\$5.0 and \$5.8 billion in 2007, respectively), most medical device product categories are niche \$50 to \$500 million market opportunities.⁹

The total endograft market size is difficult to estimate because two of the top three endograft manufacturers, Cook Medical (Bloomington, IN) and W.L. Gore & Associates (Flagstaff, AZ), are private companies whose sales data are not publicly available. Medtronic, Inc. (Minneapolis, IN), a public company and the other leader in the market, achieved global endograft (abdominal and thoracic) sales of \$285 million in their fiscal year ended April 30, 2008, and Wall Street analysts expect them to achieve growth of 16% to reach sales of approximately \$330 million for the year ended April 30, 2009.^{10,11} iData Research and Millenium Research Group, two well-known market research firms in the medical device space, each estimates that the U.S. aortic endograft market (abdominal only) will reach or exceed \$500 million by 2010.^{12,13} When combined with thoracic and international markets, the total opportunity may well already exceed \$1 billion (Fig. 2).

Venture capitalists have been active in the last decade in seeding and developing a new generation of endograft technology companies that aim to improve upon the shortcomings of existing marketed devices and expand endovascular therapy to new frontiers. Assessing the endograft market and placing strategic bets requires a venture capitalist to use a similar framework as to how a physician would assess a given patient who may be eligible for a new or emerging therapy.

PHYSICIAN: INDICATIONS AND PATIENT SELECTION;

VENTURE CAPITALISTS: INDICATIONS AND SEGMENT SELECTION

Top venture capitalists may receive 1000 to 2000 new ideas and companies a year, evaluate as many as 200 to 300 of them, and fund only 8 to 10.⁵ Thus venture capitalists need to screen opportunities quickly to qualify opportunities that deserve a closer look and dedication of time and resources.

Assume that a given set of investment opportunities each has a solid intellectual property foundation and reputable management team (two of the most important criteria for venture capitalists, which we will take for granted herein). Choosing which company or technology to invest in from this opportunity set first requires an analysis of the existing or potential market

Table 1 Historical and Recent Venture-Backed Aortic Endograft Companies

Company	Founded	Technology	VC Investors	Venture Investment (Millions of Dollars)	Exit	Status
EndoVascular Technologies, Inc.	1989	AnCure unibody endograft	J.P. Morgan Partners, Kleiner Perkins Caulfield & Byers, Mayfield Fund, Menio Ventures, Piper Jaffray Ventures, Sequoia Capital, Suez Ventures, Trinity Ventures, The Vertical Group	\$34.8	IPO February 1996 with market value of \$82.8 million; acquired by Guidant in December 1997 for \$171 million	AnCure no longer available
Prograft Medical, Inc.	1993	Excluder modular endograft	Institutional Venture Partners, St. Paul Venture Capital, Kingsbury Associates	n/a	Acquired by W.L. Gore & Associates in June 1997	FDA approved
AneuRx, Inc.	1993	AneuRx modular endograft	MedVenture Associates, Delphi Ventures, Mohr Davodow Ventures, Morgenthaler Ventures, New Enterprise Associates, Brentwood Venture Capital, Three Arch Partners, ONSET Enterprise Associates, Windspeed Ventures	\$15.2	Acquired by Medtronic, Inc. in May 1996 for \$68.6 million	FDA approved
TriVascular, Inc.	1998	Enova endograft with injectable polymer channels	ABS Ventures, Delphi Ventures, The Vertical Group, De Novo Ventures	\$19.5	Acquired by Boston Scientific in April 2005 for \$65 million in addition to its previous investments and notes issued of approximately \$45 million	Failed in clinical trials
Nellix Endovascular, Inc.	2001	Sac-anchoring prosthesis	Essex Woodlands Health Ventures, Band of Angels, Incubic Venture Fund	\$19.6	n/a	In development
Aptus Endosystems, Inc.	2002	Endograft with endostapler	U.S. Venture Partners, Prism VentureWorks, Baird Venture Partners, FirstMark Capital, Heron Capital	\$59.2	n/a	US IDE phase II trial completed February 2009
TriVascular2, Inc.	2007	Endograft with injectable polymer channels	Delphi Ventures, New Enterprise Associates, MPM Capital, Kearny Venture Partners	\$65.0	n/a	In development (redesign)

Sources: press releases, SEC filings, CapitalIQ database, VentureXpert database.
IPO, initial public offering; FDA, Food and Drug Administration.

Figure 2 U.S. endograft market size estimates. (Source: Millenium Research Group, iData Research.)

segments and the limitations of current technologies or standards of care. Venture capitalists often ask three basic initial questions: (1) Is the target market segment big enough? (2) Is there a clear clinical need or patient benefit addressed by the technology? (3) Does the technology provide time savings, ease-of-use benefits, and/or financial advantage for the physician?

The Abdominal Aortic Aneurysm Market

The largest market opportunity for endovascular technology is infrarenal abdominal aortic aneurysms (AAAs), currently about a \$400 million market in the United States alone.^{12,13} Early growth in the AAA market was constrained due to durability issues with first-generation grafts, including migrations, device kinking, stenosis/thrombosis, and suture or stent breakage.^{14,15} As technology and patient selection improved, and as compelling clinical evidence from randomized trials like the DREAM and EVAR I trials have shown the safety and benefits of endovascular repair, the AAA endograft market has continued to grow.^{16,17} In the United States, the number of endovascular repairs of AAAs is now estimated to exceed the number of open surgical repairs of AAAs (Fig. 3).

Yet the open versus endovascular debate is still a major topic at interventional and surgery meetings and a need still persists for endograft technologies that are free from migration, endoleak, and long-term durability concerns. Lower-profile, easier-to-use delivery systems are also solutions many physicians would welcome, which could markedly expand the addressable market. Looking forward, the AAA segment could grow even faster if clinical studies on early intervention for small aneurysms (4 to 5.5 cm in diameter) prove conclusive, and if screening initiatives like the recently passed SAAVE act (one-time "Welcome to Medicare" screening) reveal a large prevalence of aortic disease currently asymptomatic or undiagnosed. Incremental technological advancement and better patient selection have

resolved many of the first-generation issues, but there is still ample opportunity to improve endograft technology in more complex cases where iliac access is a concern or where infrarenal necks are short or highly angulated.¹⁸ Given the technical shortcomings of existing technologies as well as the large market currently underserved by FDA-approved endografts, the AAA endograft market is compelling for venture capital investment.

The Thoracic Aortic Disease Market

The next logical market opportunity for innovative endovascular technology is thoracic aortic disease. Open surgery for thoracic aortic disease is highly invasive and morbid, and a strong clinical benefit exists for endovascular approaches.¹⁹ With market size estimates from \$100 to \$200 million (Fig. 2), it falls below the typical \$500 million threshold for venture capital attention, but the thoracic segment is still attractive if a company can leverage technology platforms developed for abdominal aortic disease.

Figure 3 U.S. endovascular repair procedures and penetration estimates. EVAR, endovascular aneurysm repair. (Source: Millenium Research Group, iData Research.)

Within the thoracic aortic disease segment, the subsegment calculation is challenging, because the range of diseases and indications is more variable than abdominal aortic disease. The location of disease (descending, arch, ascending) and type of disease (aneurysm, pseudoaneurysm, penetrating ulcers, type B dissection, type A dissection, coarctation, trauma) affect whether a given technology platform will or will not be appropriate with minimal redesign. Vessel diameters, blood flow dynamics, visceral vessels, and arch curvature all present engineering challenges much different from the abdominal aorta. Therefore, the venture capitalist has to look at each subsegment separately and challenge companies that claim their AAA technology platform can provide solutions for thoracic aortic disease.

Niche Markets for Complex Aortic Disease

Within both the aortic and thoracic market segments, new endovascular technology is needed for the treatment of highly complex disease, including juxtarenal and pararenal aneurysms, concomitant iliac disease, and arch-located disease. Fenestrated and branched endografts, endostapling systems, and low-profile or percutaneous delivery systems all attempt to bring endovascular technology to complex cases typically reserved for surgery or otherwise left untreated.^{20,21}

From a venture capital perspective, these frontier market segments have a compelling clinical need, but the incidence of cases might be too small to justify starting a new company dedicated to providing a solution. Additionally, in the case of branch and fenestrated endografts, custom devices are often required, which are expensive to produce and may require the resources of a large company. The incumbent market participants can justify research and development (R&D) investments in these niche segments as they can leverage existing technology platforms and engineering resources. The innovation leadership and symposia attention help to strengthen their brands and solidify their core endograft businesses. Indeed, while Medtronic, Cook, and Gore all have funded branch and fenestrated graft development programs, there are currently no startups directly pursuing this technology as their core focus.

The Endoleak Market

Another aortic disease market segment a venture capitalist could consider is the treatment of postoperative complications, most notably endoleaks. The incidence of type I, III, and IV endoleaks is relatively low, which limits the overall opportunity. Treatment for type I and III endoleaks are also typically resolved with an additional endograft component readily available from manufacturers, or surgery in some cases.²² The incidence of

type II endoleaks is larger, estimated at 25%, but the actual clinical significance of these endoleaks remains debatable.²² Coils and glues used to treat type II endoleaks can sell for \$1000 to \$1500, significantly lower than the \$10,000 to \$12,000 price tags for endografts. A back of the envelope calculation might go something like this: endoleak maximum market potential = (40,000 endovascular AAA procedures) * (20% incidence of type II endoleaks) * (\$1000 to \$1500 device price) = \$8 to \$12 million maximum U.S. market potential. This is simply not a big enough market for a venture firm who needs to invest in large market opportunities with the expectation of home run returns to satisfy the LP investors in the fund. For physician innovators or small companies with novel endoleak solutions, the alternative to seeking venture capital investment might be to license or codevelop with a large company already in the space. The better quest for a venture capitalist is to find an endograft technology that prevents endoleaks in the first place, rather than focusing on how to fix them postoperatively.

PHYSICIAN: IMAGING AND PREOPERATIVE PLANNING; VENTURE CAPITALIST: DUE DILIGENCE AND PREINVESTMENT PLANNING

Once the venture capitalist has appropriately sized and segmented the market opportunity and defined the clinical needs and limitations of existing technology, he or she can turn his or her attention to emerging technologies and specific investment opportunities. One primary aim of due diligence is to assess the market adoption potential of a given technology or product. Besides spending a considerable amount of time doing technical and engineering due diligence and evaluating bench, preclinical, and clinical data reports, venture capitalists talk at length to key opinion leaders and high-volume practitioners about the adoption potential of specific technologies and the limitations of current standards of care. Looking at the current landscape of venture-backed endograft companies, one can speculate as to the key questions that arose for each technology that affected the investment decision for the venture firms that may have performed due diligence (whether or not they invested).

Endostapling Technology

What is the true market opportunity for endostapling technology? If used only for redo procedures in case of migrating or migrated endografts, the market opportunity would only be the estimated (0.5 to 5%) of cases annually that require this secondary intervention and clearly not what the companies and their venture backers set out to accomplish.²³ The real opportunity is coupling endostapling technology with a complementary

endograft as the primary method of aorto-graft fixation, as in the case of the AptusTM Endovascular AAA Repair System. For endostapling technologies, the due diligence questions might include: is this a niche technology that will only be used in cases where the physician thinks fixation will be a problem (e.g., short necks or angulated necks)? If so, how reliably does the endostapler perform in severely angulated cases or in cases where aortic purchase may be an issue due to the presence of calcium or thrombus? Or will the technology become a preferential device to be used for straightforward cases as well as more complex cases? How much additional time, if any, does the use of an endostapler add to the procedure? Is there a chance of misfiring the staple and having it embolize? What about the long-term durability of the staples? Will they stay in place through mechanical and bioincorporation forces? Is the endostapler intuitive and easy to use? Is the endograft itself immune from first-generation endograft problems like kinking, graft material degradation, or component decoupling?

Percutaneous Endografts

TriVascular (now TriVascular2) and Nellix Endovascular are two examples of venture-backed companies offering entirely new approaches to endograft design than the traditional fabric-covered metallic stent structure. TriVascular2 has developed an innovative unibody design with an injectable polymer that fills sealing rings at multiple levels during deployment and later hardens to provide support to the body of the endograft (in place of stent structures). See <http://www.trivascular2.com> for more information. Nellix Endovascular is developing a “sac-anchoring prosthesis” technology that creates a channel for blood flow while filling in the sac with a bag filled with an injectable substance. See <http://www.nellix.com> for more information.

Both innovative designs allow the technologies to be delivered at a very low profile (12- to 16-French), which would permit delivery through calcified and narrow iliac arteries where other larger-profile delivery systems often cannot pass and perhaps usher in the era of truly percutaneous endograft repair.

For these technologies, there are numerous due diligence questions related to the technical and design aspects, but the same adoption questions apply: Will they be easy to use and deliver? What safety or efficacy issues may emerge through the use of the injectable materials? Will they become niche devices only used for certain complex cases, or will they become preferred endografts for all endovascular cases? Will these devices expand the addressable market for endovascular repair and increase penetration into cases typically selected for surgical repair? If approved, will physicians adopt the devices readily, or will they wait for clinical data that prove long-term durability?

PHYSICIAN: CONTRAINDICATIONS TO THERAPY;

VENTURE CAPITALIST:

CONTRAINDICATIONS TO INVESTMENT

The market opportunity has been vetted, and a venture capitalist feels confident about the value proposition and adoption potential of a specific company's technology or product. Now the focus turns to the path to commercialization and the future competitive landscape.

Clinical and Regulatory Path

There are two primary regulatory paths for medical devices: 510(k) and PMA. A 510(k) is typically the easier, less costly path and requires that the company show that their device is “substantially equivalent” to a previously 510(k)-approved product on the market. A clinical trial is sometimes required, but usually not. A 510(k) can typically gain approval within 3 months of filing. The advantage of a 510(k) is speed and lower cost, but the disadvantage is that there are fewer barriers to entry for competitor devices. It is worth noting that at the time of publication, there is a tremendous amount of turmoil in the medical device regulatory world around the appropriateness of the 510(k) pathway, especially for implantable or nontrivial risk devices. The public policy debate is active, and in the coming years the FDA may require clinical trials to prove safety and efficacy for all but the most trivial of devices. This will increase the costs and time required to reach commercialization and factor into the venture capital equation.

The PMA regulatory route is more complex and requires a clinical trial with specific safety and efficacy thresholds and can take upward of 2 years or longer to receive approval. The disadvantage of a PMA is the length of time and significant expense required, but the advantage is that once approved, there are high barriers to entry for others seeking to get into the market (they also have to go the PMA route). To date, all endografts in the United States have fallen under the PMA route. In the endograft space, a venture capitalist must estimate the investment and time required to run a PMA clinical trial and receive approval. Historically speaking, endograft PMA trials have been notoriously long, and it has become increasingly difficult to consent and enroll patients when commercially available endograft alternatives exist (Table 2).

Reimbursement

FDA approval is only the first step on the path to commercial and investment success. Increasingly, acquirers and public market investors want to see established reimbursement for novel medical devices, and thus venture capitalists want to clearly understand the reimbursement strategy during their due diligence. For most

Table 2 Time from Pivotal Trial to FDA Approval

Company/Product	1st Patient, Pivotal U.S. Trial	FDA Approved	Time Lapse (y)
Medtronic AneuRx	April 1997	September 1999	2.5
Gore Excluder	December 1998	November 2002	3.9
Gore TAG Thoracic	September 1999	March 2005	4.6
Cook Zenith	January 2000	May 2003	3.4
Endologix Powerlink	July 2000	October 2004	4.3
Medtronic Talent	February 2002	April 2008	6.3
Medtronic Talent Thoracic	December 2003	June 2008	4.6
Cook TX2 Thoracic	April 2004	May 2008	4.2

Source: company websites, clinicaltrials.gov, press releases.
FDA, Food and Drug Administration.

novel medical devices, the reimbursement pathway can be long, arduous, and highly fragmented. As opposed to the FDA, which provides central regulatory approval, there is no central pathway to reimbursement approval. Before the Center for Medicare and Medicaid Services (CMS) or most commercial insurers will even consider reimbursing a new procedure, they usually require American Medical Association and subspecialty buy-in, multiple peer-reviewed journal articles, thought leader presentations and testimonials, and economic cost-benefit analyses. Once these assets are in place, each of the 11 CMS regional bodies and each private insurer must be independently lobbied for reimbursement rates. In the case of new aortic endografts, this is less of an issue as new technologies will be able to draft off of existing reimbursement paradigms for endovascular aneurysm repair. To the extent that novel technologies fall outside of established reimbursement codes, the venture capitalist will factor this into their investment decision.

Competitor Strength and Product Pipelines

FDA approval and reimbursement are not necessarily the panacea: the venture capitalist must also assess the likelihood of market adoption in the face of strong competition from incumbents, many of whom have sponsored training for surgeons and interventionalists and retain some measure of company or product loyalty.

The aortic endograft market is dominated by three large incumbents (Medtronic, Cook, and Gore) and a fourth emerging player (Endologix, Irvine, CA). Sales reps from these companies are highly trained and a valuable resource in the pre-case planning and intraoperative environment. Venture-backed companies have significant incumbent relationships to overcome in getting their new devices trialed, or they must spend significant sums of money to train and hire experienced sales reps.

Compounding the problem of strong incumbent relationships is the fact that these companies are also spending heavily on R&D to develop new products. An analysis of press releases and other publicly available information reveals a strong new product pipeline for these companies (Table 3).

A venture capitalist must assess this pipeline vis-à-vis their investment opportunity. Does the startup company have an incremental or leapfrog technology? For example, do they have an incrementally better profile advantage (16- to 18-French) or a leapfrog advantage (12-French or less)? In either case, for how long might they have market exclusivity before the incumbents' product development efforts catch up? Would the incumbents be better off buying the startup or developing on their own? Because the development and regulatory timelines are so long in the endograft space, trying to anticipate what the competitive landscape will look like upon approval is difficult. What appears to be an

Table 3 Endograft Pipelines

Company	Product	Status
Abdominal		
Lombard Medical (Oxfordshire, UK)	AorFix	U.S. trial initiated October 2006; approved OUS
Aptus Endosystems	Aptus AAA Repair System	U.S. trial initiated September 2007
Medtronic	Endurant	U.S. trial initiated June 2008; approved OUS
Cook	Zenith LP	U.S. trial initiated October 2008
Thoracic		
Medtronic	Valiant	U.S. trial initiated December 2006
Bolton (Sunrise, FL)	Relay	U.S. trial initiated January 2007
Cook	Zenith Dissection	In EU clinical trials

Sources: press releases, clinicaltrials.gov, company websites.
OUS, outside the United States.

advantage today may not be so in a few years time. For example, endostapling technology is a compelling solution to the migration problem, which perhaps was one of the clinical need targets that startup companies were founded to address. But many physicians now argue that the migration problem is no longer a big issue now that technique and patient selection has improved. On the other hand, endostapling may allow for safe and effective endovascular repair in patients with aneurysm anatomies that would currently require open repair due to limitations of commercially available endografts.

PHYSICIAN: OUTCOMES; VENTURE CAPITALIST: EXITS

Venture capitalists often look at historical exits and valuations before making their first investment in a company. Indeed, research has shown that market entry (new companies) is positively associated with prior merger and acquisition (M&A) activity in the sector, the number and valuation of prior IPOs for firms in that sector, and the amount of venture capital funding invested in firms in that sector.²⁴ Despite a historically active M&A market, successful exits of venture-backed companies dedicated to the endovascular repair of aortic disease are artifacts of history and produced few “home runs.” There has only been one IPO of a venture-backed endograft company, over 10 years ago, and there has never been a venture-backed exit of a private company with a valuation in excess of \$100 million (remember that the cost to develop and commercialize a medical device is estimated at \$40 to \$100 million). Other companies that were financed through corporate investments or other nonventure forms of financing also had exits typically in the sub-\$100 million range (Table 4).

Compounding the historical problem is the current relative lack of acquirers for endograft technologies. Cook and Gore both have a reputation for developing new technology in-house or in collaboration with physicians rather than acquiring startup companies. Medtronic

acquired AneuRx in 1996 and inherited the Talent endograft from its acquisition of Arterial Vascular Engineering in 1999, but it has concentrated on in-house development ever since and has not made any minority equity investments in startup endograft companies as it tends to do in other markets. All three of these market leaders are less attractive exits to venture investors anyway, as valuation is a function of cannibalization for incumbent market participants—they are less likely to make their own technology obsolete.²⁴ It is difficult to justify a high acquisition price premium when buying a technology that will cannibalize some amount of an existing sales base. For a nonincumbent, the valuation premium could be much higher because they would get the full benefit of the new revenue stream. Venture capitalists must assess all of these exit scenarios and likely valuations even though the exit itself may be years away.

PHYSICIAN: COMPLICATIONS; VENTURE CAPITALIST: COMPLICATIONS

EndoVascular Technologies, Inc., which was acquired by Guidant Corporation in 1997, experienced a series of malfunctions with the delivery system of their AnCure device after FDA approval in 1999. After failing to report these malfunctions while promoting an untested technique to resolve the malfunctions, Guidant shut down the division and eventually entered into a plea agreement with the U.S. Department of Justice in 2003 and made a payment of \$43.4 million with an additional \$49 million civil settlement. The gross misconduct of the corporation resulted in one of the first guilty pleas to criminal felony convictions.²⁵ Although the original venture capital investors had exited the company via IPO before these problems arose, you can be sure the bar was raised much higher for all future investment opportunities in which presumably minor technical issues could literally cause the failure of a company.

The original TriVascular spent 9 years and over \$20 million of venture capital money and an additional

Table 4 M&A and IPO Activity of Aortic Endograft Companies

Date	Company	Product	Exit	Value (Millions of Dollars)
February 1996	EVT	Ancure	IPO	\$82.8
April 1996	AneuRx	AneuRx	Acquired by Medtronic	\$68.6
May 1996	MinTec	Vanguard	Acquired by Boston Scientific	\$72.0
June 1997	Prograft Medical	Excluder	Acquired by W.L. Gore	n/a
October 1997	EVT	Ancure	Acquired by Guidant	\$171.0
April 1998	World Medical Mfg Corp	Talent	Acquired by AVE	\$62.0
December 2001	TERAMed	Ariba/Quantum	Acquired by J&J Cordis	n/a
May 2002	Endologix	Powerlink	Merged with Radiance Medical	\$33.0
February 2005	Endomed	EndoFit	Acquired by LeMaitre Vascular	\$4.1
April 2005	TriVascular	Enova	Acquired by Boston Scientific	\$65.0

Sources: SEC filings, press releases, CapitalIQ.

M&A, merger and acquisition; IPO, initial public offering; EVT, Endovascular Technologies, Inc.; AVE, Arterial Vascular Engineering.

undisclosed amount of funding from Boston Scientific (Natick, MA) before encountering problems with their Enovus endograft. After the company was acquired by Boston Scientific in 2005, the phase II clinical trial was halted in 2006 after experiencing at least two dozen stent fractures, and in 2007 the FDA warned Boston Scientific and its TriVascular subsidiary about inadequate record-keeping and reporting following five patient deaths in the trial.²⁶ Again, the venture capitalist investors escaped significant financial harm through the exit to Boston Scientific in 2005, but they obviously highlighted the failure of due diligence to uncover or anticipate the stent fracture issue and they also failed to recoup the \$31 million earn-out portion of the acquisition deal (an earn-out is a portion of the acquisition proceeds that are paid contingently upon achievement of certain milestones, for example, regulatory approval or sales benchmarks).²⁷

Many other endograft technologies have failed post-acquisition as well, including Boston Scientific's \$72 million acquisition of Mintech Inc. and the Vanguard device in 1996, which was widely used in Europe but never introduced in the United States due to poor results in a controlled clinical trial.²⁸ Johnson & Johnson's Cordis division (Warren, NJ) acquired TERAMed in 2001 but the Fortron/Quantum endograft never achieved FDA approval and was pulled from international markets. Arterial Vascular Engineering acquired World Medical Manufacturing Corp.'s Talent endograft in 1998, and was subsequently acquired by Medtronic in 1999. Although the Talent endograft has been successfully marketed internationally since 1998 and in fact has been an international market leader for much of the past decade, it has only been available in the United States since 2008 due to an extremely long approval process stemming from undisclosed issues. Many physicians had expected this device to be approved in the United States as early as 2003, and so presumably did Medtronic and Arterial Vascular Engineering in their acquisition valuation models. Edward's Lifesciences (Irvine, CA), which had previously acquired technology from Endogad Research Pty. Limited, tried to sell their Lifepath endograft in 2003, and after failing to find a buyer, it was discontinued in 2004.²⁹ Terumo Corporation of Japan acquired Sulzer Vaskutek Ltd. in 2002 and inherited the Anaconda endograft, which is available internationally but has yet to begin a U.S. pivotal trial. All cases of buyer beware and examples of how notoriously difficult it is to successfully commercialize endograft technologies.

All of these endograft failures have forced today's potential acquirers to be much more rigorous in their own due diligence before making acquisitions in the endograft space. Having learned from previous failures, potential acquirers are forcing startups and their venture investors to spend more time and more money proving the viability of their technologies before entertaining an acquisition. This puts more pressure on venture capital-

ists to reserve enough "dry powder" for follow-on investments, which highlights the opportunity cost of not investing in other promising opportunities with those same funds. They also must endure longer holding periods before exiting their investments, which means it takes longer to show returns to their own demanding LP investors.

CONCLUSION

Venture capitalists are in the business of taking big risks in the expectation of big rewards. On the reward side, the endovascular repair of aortic disease represents an opportunity with significant potential: an existing market in excess of \$1 billion, compelling growth for the foreseeable future, and the need for more advanced technology solutions to overcome the limitations of existing devices and expand treatment to complex abdominal and thoracic aortic disease segments. Many venture capitalists are also intrigued by the potential of percutaneous endografts in terms of customer base. Sub-12-French devices negating the need for a surgical cutdown could be marketed and sold to a wider customer base.

On the risk side, this market has many: a long PMA regulatory path with expensive clinical trials, strong incumbent competitors with solid new product pipelines, and a history of failed devices and relatively small exits. These risks may deter many venture capitalists, but that does not necessarily mean innovation will slow or cease in the aortic disease market. Venture capital is just one innovation pathway for opportunities that meet certain criteria. Alternative forms of financing may be available with different criteria, including government programs and high-net-worth individuals. Physician innovators and engineers can license or sell their intellectual property and work directly with established companies rather than try to start new companies and perhaps get to market even sooner by leveraging established expertise, resources, and infrastructure. The market leaders will continue to invest in research and development informed by physician customers and consultants. All are viable pathways to innovation.

And just as innovation is not solely reliant on venture capital, the future of aortic disease is not solely reliant on endografts. Advances in imaging technology and postoperative monitoring may negate the need for costly and repetitive computed tomography scanning. Advances in robotic surgery and hybrid endovascular and open surgery techniques will open new frontiers for surgeons. Research done by Frederico Parodi and colleagues on matrix metalloproteinase inhibitors might point to the future of endovascular repair via a biologic solution.³⁰ Early detection with smoking cessation and healthier lifestyles could markedly reduce the overall burden of aortic disease and represent an innovation in prophylactic management. Until then, the venture

capital community will be monitoring the progress of recent venture-backed companies like TriVascular2, Nellix, and Aptus Endosystems to see if they can overcome historical barriers to success and produce returns for patients and investors alike.

DISCLOSURE

Dr. Resnick is an investor at Prism VentureWorks, a venture capital firm. Prism VentureWorks is an investor in Aptus Endosystems, Inc.

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