Integration of Clinical Practice, Research, Innovation, and Education

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Introduction

Modern aortic programs require integration of clinical practice, research, innovation, and education (Fig. 15.1). It is critical for physicians to develop collaborations between multiple specialties, engineers, and industry. More important is the need to constantly assess outcomes and to identify weaknesses and strengths. Changes in a procedure, methodology, or concept require analysis of outcomes and dedicated time to develop a team approach to address complex problems. This is well exemplified by the experience and legacy of Dr. Roy Greenberg (1964–2013), our friend, teacher, and a pioneer in fenestrated and branched techniques. This chapter summarizes the evolution of Dr. Greenberg's major contributions to modern aortic therapy, and how his influence affected the development of advanced clinical and research programs at Cleveland Clinic and worldwide.

Dr. Roy Greenberg's Legacy

Investing in Education

A fundamental aspect is the time invested in education and training, which cannot be shortened to achieve outstanding results. Despite being a gifted technician, Dr. Greenberg sought himself specialized training, well beyond the traditional paradigms for early 1990s. His background included biomedical engineering (Cornell University, 1987), a Medical Degree (University of Cincinnati, 1992), and general surgery training (University of Rochester, 1997). He realized the importance of mastering endovascular skills and sought an interventional radiology fellowship in Sweden (1998) before obtaining his vascular surgery training at the University of Rochester (1999).

Early Years

Dr. Greenberg joined the staff of the Cleveland Clinic in 1999. His initial approach was to generate an exceptionally busy clinical practice (Fig. 15.2) that consisted largely of complex aortic problems, while coupling this with his efforts in research and development. He contributed significantly to the dissemination of advanced endovascular techniques, including numerous landmark publications (Table 15.1), research grants, and over 50 published patents [1–16]. Some of his most important contributions ranged from novel stent-graft designs to mathematical modeling of three-dimensional imaging and numerous aspects of fenestrated and branched endograft techniques.

Identifying Clinical Need

Roy developed several physician-sponsored investigational device exemption (IDE) protocols, which allowed him to have access to technology not yet commercially approved in the United States, while conducting high-quality prospective clinical trials to evaluate outcomes of fenestrated and branched stent-grafts. As a result, he accumulated the largest worldwide experience in essentially every advanced aortic technique. In addition to a robust clinical experience, Dr. Greenberg research laboratory focused among other things on the development of more durable branch stent-grafts. His designs incorporated features that he felt would mitigate the

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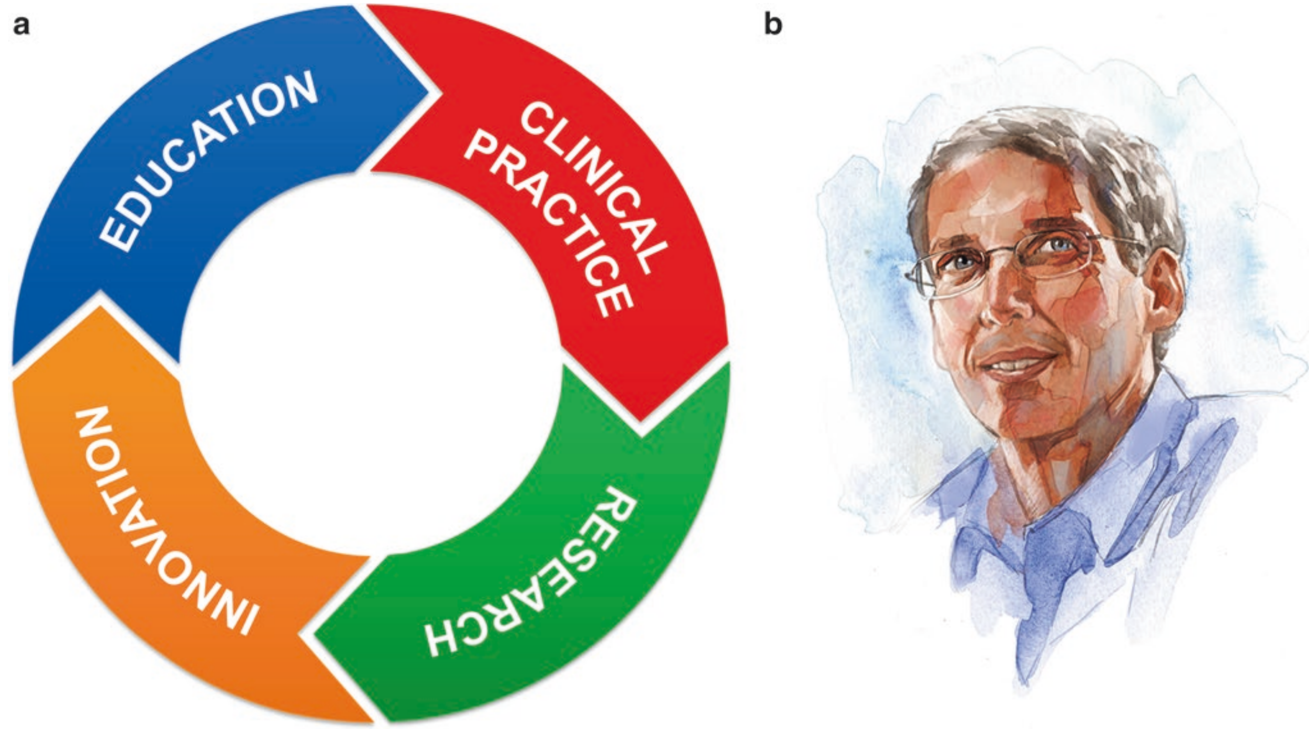


Fig. 15.1 An integrated aortic program with clinical practice, research, innovation, and education (**a**) as modeled by Dr. Roy K. Greenberg at the Cleveland Clinic (**b**). By permission of Mayo Foundation for Medical Education and Research.

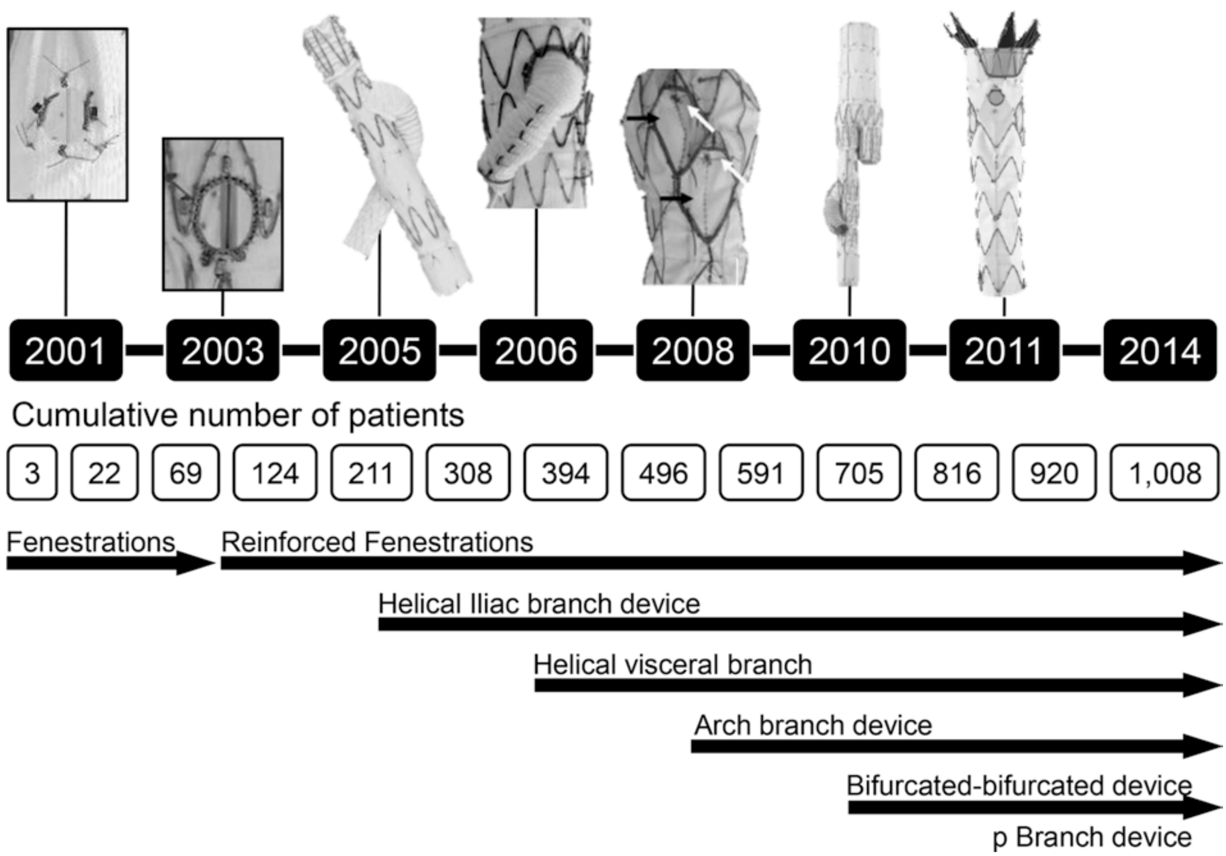


Fig. 15.2 Progress of clinical practice and branch incorporation in Dr. Greenberg's physician-sponsored investigational device exemption protocols. Reproduced with permission from Oderich GS. New Horizons in Aortic Disease The Lasting Legacy of a Visionary Innovator. J Endovasc Ther. 2015; 22(1): 139–145

Table 15.1 Selected landmark publications on fenestrated and branched techniques by Dr. Greenberg and colleagues[a]

First author (year)	Study design	Main message
Greenberg [3] (2004)	Prospective study of fenestrated repair for juxtarenal AAAs	• Fenestrated repair is safe and effective • Low rate of type I endoleak (<1 %)
Haddad [1] (2005)	Renal outcomes during fenestrated EVAR	• Renal function deterioration occurred in 32 % of patients with plateau at 3 months
O'Neill [2] (2006)	Prospective study of fenestrated repair for juxtarenal AAAs	• Fenestrated repair is safe (1 % mortality) and effective at midterm follow-up of 17 months
Goel [6] (2008)	Mathematical analysis of DICOM datasets	• Automated mathematical model is feasible and reproducible to calculate inter-renal distances compared to experienced operator
Dowdall [8] (2008)	Separation of components in fenestrated and branch endovascular repair	• Intercomponent movement (>10 mm) was noted in 14 devices, 8 of which had <2-stent overlap per IFU • Rate of type III endoleak was <1 % • 4-stent overlap was protective in all patients
Mohabbat [7] (2009)	Renal fenestration patency and duplex velocity criteria for stenosis	• Peak systolic velocity of 250 cm/s and renal-aortic ratio >4.5 suggested as criteria for renal stenosis >60 % • Covered stents associated with improved patency rates
Conway [17] (2010)	Renal implantation angles in TAAAs	• Type IV TAAAs more often have downward-going renal arteries • Types II and III TAAAs more often have orthogonally oriented renal arteries • Data support use of fenestrated branches for renal arteries
Bub [20] (2011)	Cardiac events during fenestrated and branched endovascular repair	• Atrial fibrillation in 9 %, myocardial infarction in 7 %, ventricular arrhythmias in 3 %, and cardiac death in 2 % • Troponin elevation in 12 % • Preoperative stress was not predictive
Dijkstra [11] (2011)	Cone-beam CT in fenestrated endografts	• Decreased contrast dose and fluoroscopy time • Immediate detection of technical problems may decrease rate of reinterventions
Pannucio [12] (2011)	Indirect vs. direct radiation doses during fenestrated TAAA repair	• Fluoroscopy time is unreliable to measure radiation exposure • Effective radiation dose of TAAA repair is equivalent to 2 CT studies and a single operator can perform 300 cases before reaching maximum operator dose
Brown [13] (2013)	Family history of aortic disease	• Family history predicted higher rates of aneurysm in every segment of the aorta • Patients with family history are younger and over 50 % ultimately developed suprarenal involvement
Mastracci [16] (2013)	Branch durability	• 89 % freedom from any branch-related reintervention at 5 years • Death from branch-related complications is rare (<0.5 %) • Renal occlusion is infrequent (<1.7 %) with renal fenestrated branches
Qureshi [19] (2012)	Outcomes of fenestrated repair in patients with COPD	• Severe COPD associated with decreased long-term survival • Patients with COPD had lower endoleak rates and more sac shrinkage
Oderich [17] (2014)	United States Zenith Fenestrated Pivotal Trial	• First multicenter study leading to commercial approval of the Zenith fenestrated device in April 2012 • 30-day mortality of 1.5 % with no rupture, dialysis, conversion, or early type I endoleak • Renal occlusion was 3 % • One late type I endoleak occurred at 3 years from progression of aortic disease

AAA abdominal aortic aneurysm, *EVAR* endovascular aneurysm repair, *DICOM* Digital Imaging and Communications in Medicine, *IFU* instructions for use, *TAAA* thoracoabdominal aortic aneurysm, *CT* computed tomography, *COPD* chronic pulmonary obstructive disease
[a]Reproduced with permission from Oderich GS. New Horizons in Aortic Disease The Lasting Legacy of a Visionary Innovator. J Endovasc Ther. 2015; 22(1): 139–145

risk of late failure, such as short length, long overlap, and vector alignment (Fig. 15.3). The concept of helical branches incorporated all these features by allowing alignment to the target vessel and longer overlap at the cuff. Later, this clinical experience was reported by Mastracci and colleagues (Fig. 15.4), who demonstrated 89 % freedom from any branch-related event at 5 years and remarkably low renal branch occlusion (<2 %) [2].

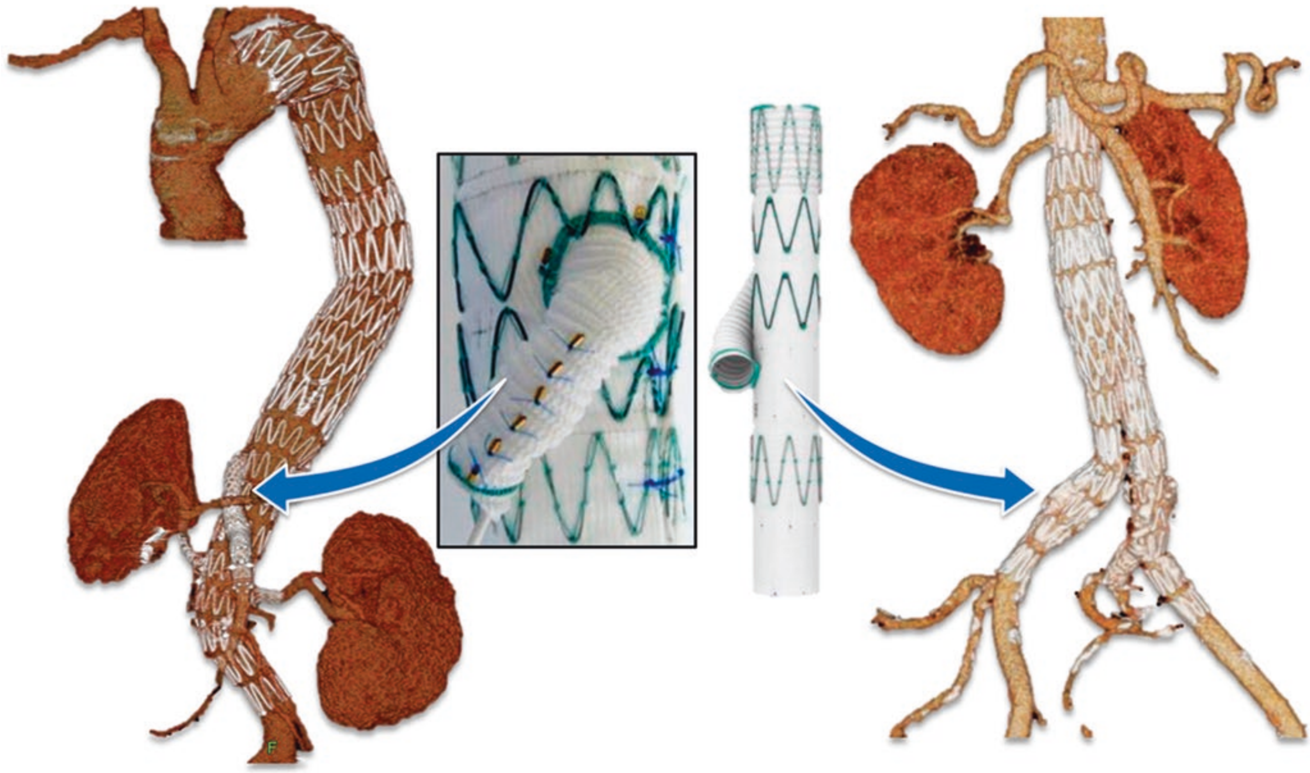


Fig. 15.3 Helical branch designs for the visceral arteries and iliac arteries. Dr. Greenberg's design for thoracoabdominal aortic aneurysms most often consisted of helical branches for the celiac axis and superior mesenteric artery with short renal fenestrated branches. Reproduced with permission from Oderich GS. New Horizons in Aortic Disease The Lasting Legacy of a Visionary Innovator. J Endovasc Ther. 2015; 22(1): 139–145

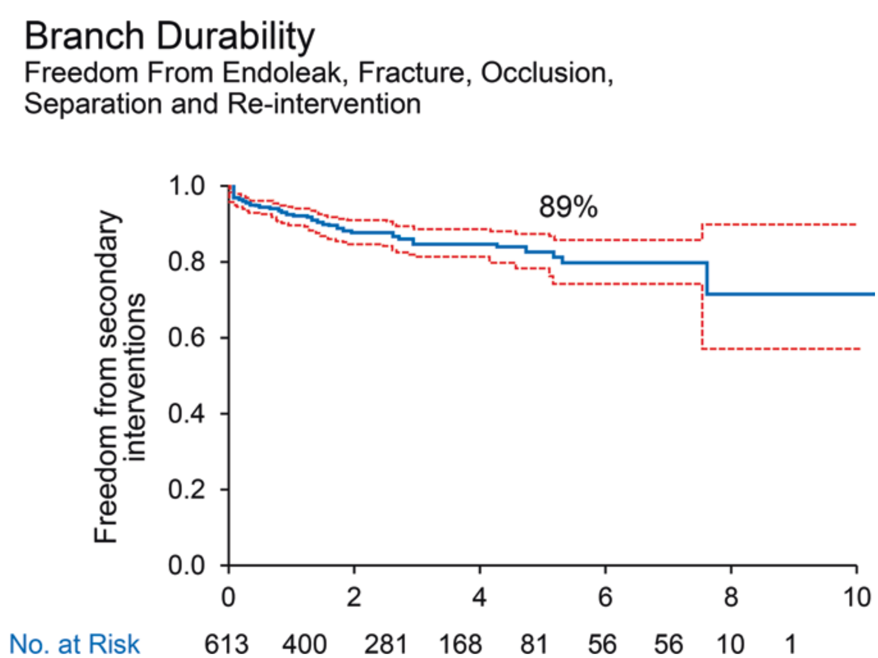


Fig. 15.4 Kaplan–Meier estimates of survival free of any branch-related complications or reinterventions including a composite of disconnection, endoleak, kink, stenosis, or occlusion. Reproduced with permission from Oderich GS. New Horizons in Aortic Disease The Lasting Legacy of a Visionary Innovator. J Endovasc Ther. 2015; 22(1): 139–145

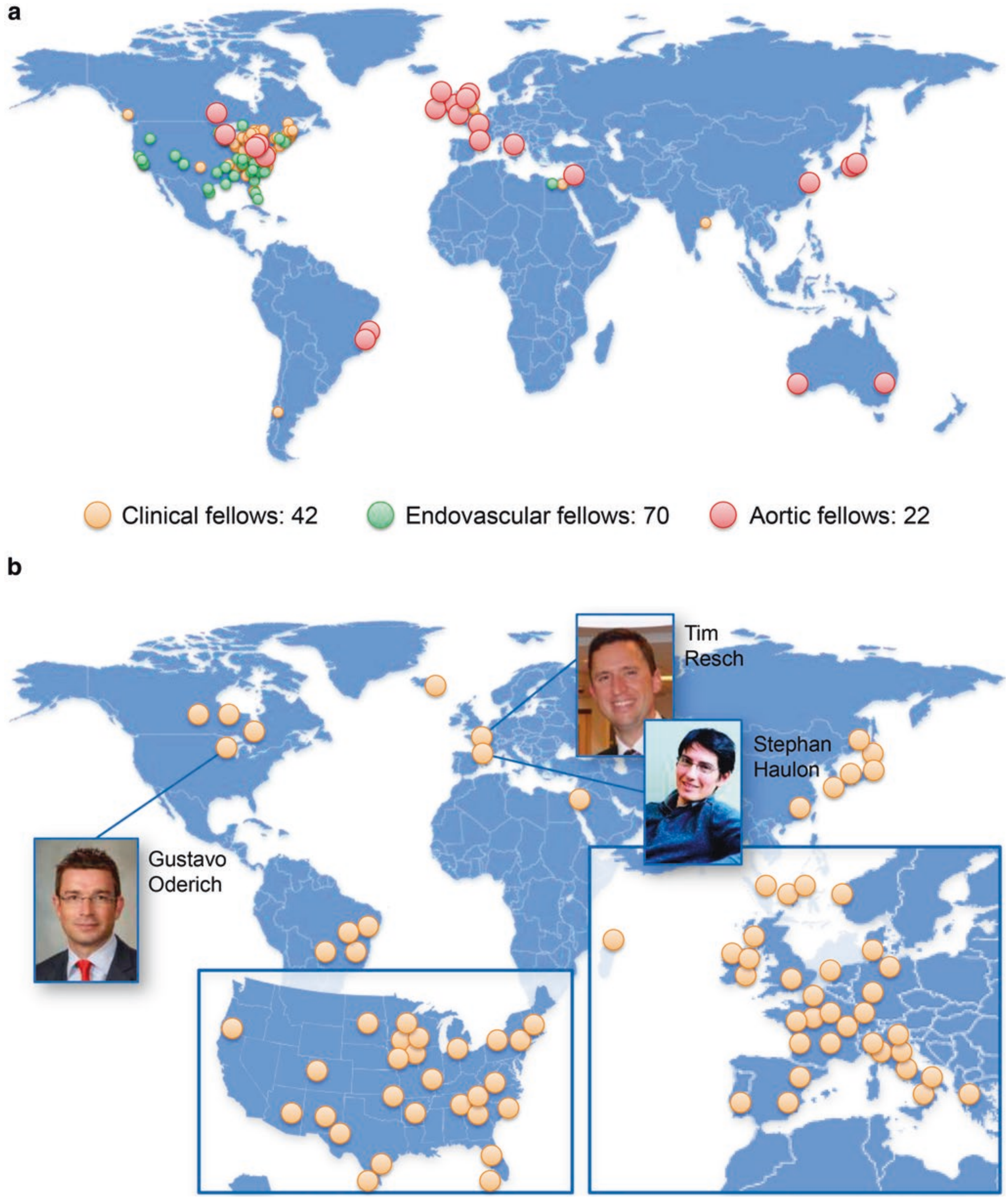


Fig. 15.5 Distributions of graduates of vascular and endovascular training programs at the Cleveland Clinic (**a**) and subsequent exponential effect on training by three of his graduates (**b**). By permission of Mayo Foundation for Medical Education and Research. All rights reserved

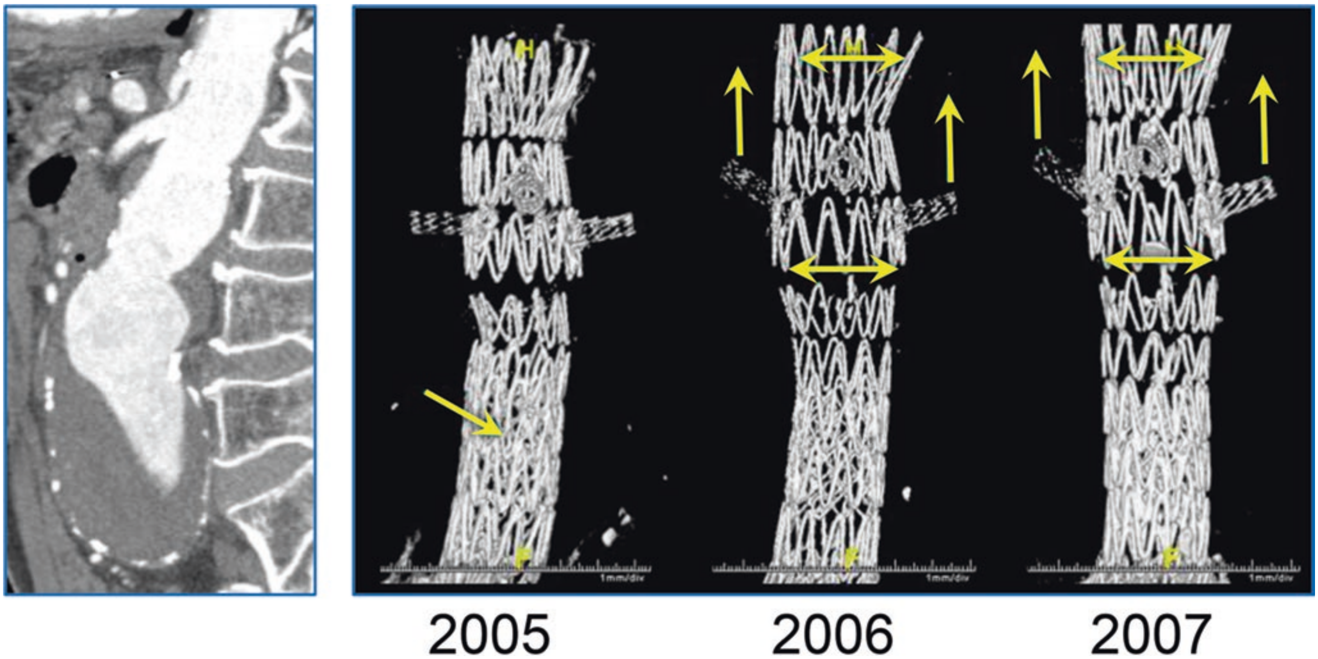


Fig. 15.6 Disease progression in a patient treated by fenestrated endovascular repair. By permission of Mayo Foundation for Medical Education and Research.

Dissemination of Endovascular Education

Dr. Greenberg's major long-lasting legacy was his contribution to education and dissemination of complex endovascular techniques. As pointed out by Dr. Ken Ouriel "An excellent surgeon enhances the lives of many patients one patient at a time, but an excellent teacher improves the lives of countless of patients in an exponential fashion". In the course of a decade, Dr. Greenberg had a direct hand in the training of 133 fellows, including 42 clinical fellows, 70 endovascular fellows, and 22 aortic fellows from all over the world (Fig. 15.5). The effect of his influence in endovascular education spread exponentially worldwide.

Focus on Durability

Dr. Greenberg always emphasized the importance of planning a durable repair that would last the patient's lifespan, well beyond 5–10 years. Based on extensive clinical experience, Dr. Greenberg recognized that placement of endografts in vulnerable aortic segments (Fig. 15.6) would be prone to late failure due to progression of aortic disease leading to device migration or loss of attachment seal. Similar to other pioneers, Dr. Greenberg's clinical practice evolved with the notion that fenestrated endografts had to be placed in more stable aortic segments, often above the celiac axis, thereby providing a more durable repair and also an alternative for future treatment in the event of failure. Based on his experience and of others, seal zones have been extended more proximally to incorporate all four vessels into a more stable aortic segment, particularly in those patients with long life-expectancy, family history of aortic disease, multiple affected segments in the aorta, prior failed open or endovascular repair, or diseased, ecstatic, or thrombus-laden necks [3, 4].

Impact on Advanced Endovascular Aortic Programs Worldwide

The Cleveland Clinic experience led by Dr. Greenberg serves as a model of modern aortic practice where clinical excellence, research, innovation, and education work synchronously. Successful programs have build their clinical experiences in a stepwise fashion with increase in the level of complexity of device design and extent of repair, higher number of TAAAs and 4-vessel designs (Fig. 15.7). It is important to learn the basic tenets of fenestrated and branched techniques in the lower risk territories (e.g., aortoiliac and pararenal aorta), and then have the courage to advance therapy to patients with more complex anatomy (e.g., thoracoabdominal aorta and arch). The extensive experience accumulated by the Cleveland Clinic group and others have demonstrated that the incremental challenge in device design complexity from two- to four-vessel fenestrations was not associated with added risk of mortality.

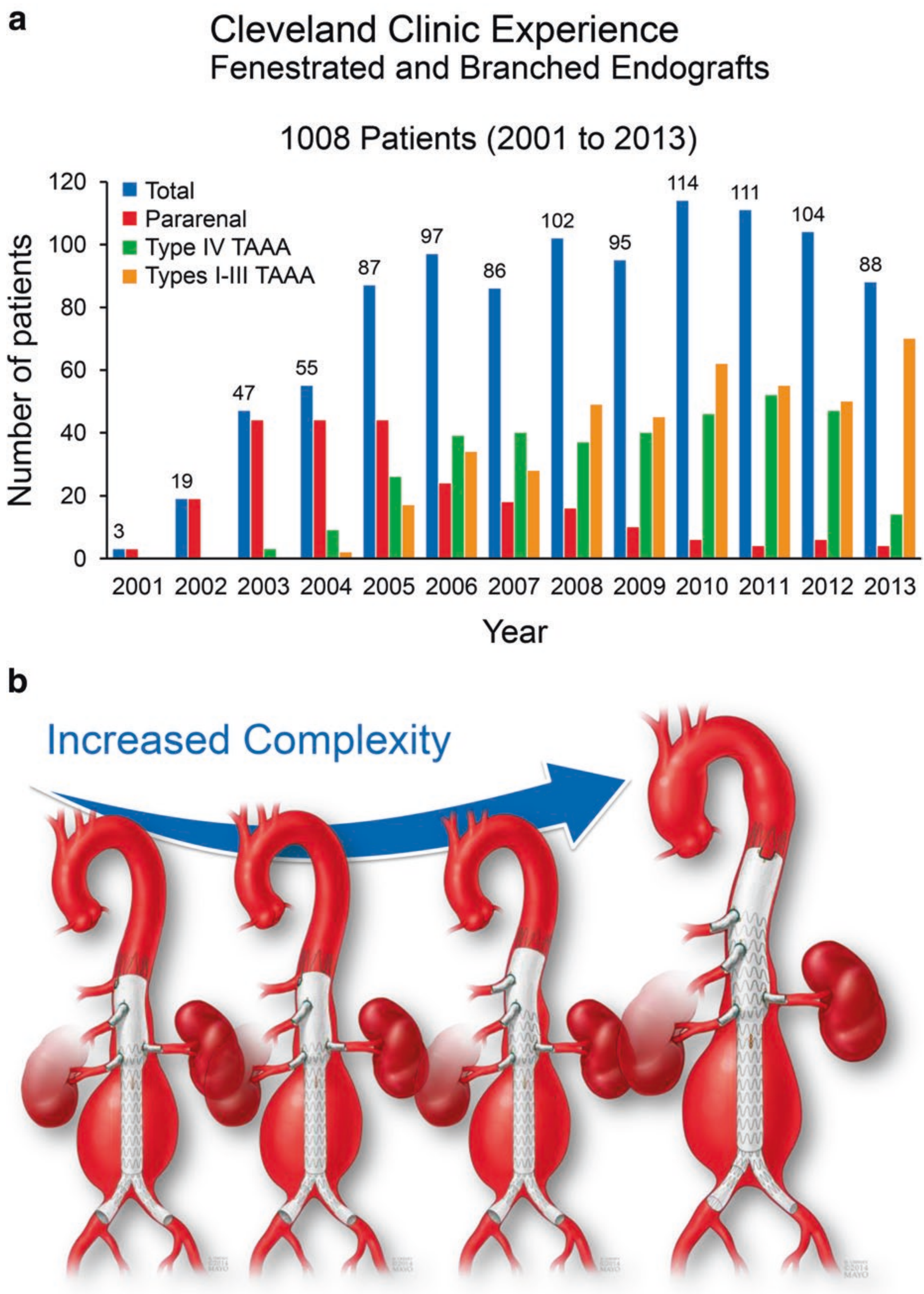


Fig. 15.7 Increasing fenestrated-branched design complexity over the years of experience at the Cleveland Clinic Foundation (**a**). For the same extent aneurysm, four-vessel designs have been used preferentially to seal the aneurysm in a more stable aortic segment (**b**). By permission of Mayo Foundation for Medical Education and Research.

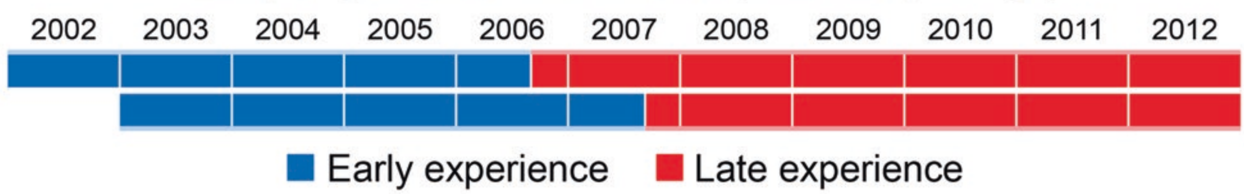
The importance of a dedicated and intensive training program in fenestrated and branched techniques is reflected by the excellent clinical results achieved by several of Dr. Greenberg's aortic fellows, who went to develop specialized aortic centers with focus on these techniques. Drs. Haulon (France) and Resch (Sweden) are examples of successful trainees who became leaders in the field [6]. In a recent report, Resch and Haulon compared outcomes of their first 50 patients treated by fenestrated endografts for juxtarenal abdominal aortic aneurysms with their contemporary experience (Fig. 15.8). There was a significant increase in utilization of three- and four-vessel designs over time. In that study, despite the increments in complexity of device design, there was significant decrease in fluoroscopy time, contrast volume, and no change in mortality (2 %).

The Mayo Clinic fenestrated program started April 11, 2007, a week after the author returned from the Cleveland Clinic for specialized endovascular training. Since then, a total of 300 patients were treated using fenestrated and branched endografts for pararenal aneurysms in 45 % and TAAAs in 55 %. There was significant increase in complexity of aneurysm extent and device design over time, which is reflected by the higher number of TAAAs and 4-vessel designs in recent years. Despite this, 30-day mortality was 2.3 % for the entire cohort, 0.6 % for pararenal, and 4.4 % for TAAAs, with no increase in mortality associated with more complex designs. In a recent analysis of the first 110 patients enrolled in a prospective non-randomized study (65 % TAAAs), there was no mortality, conversion, or aneurysm rupture.

The Mayo Clinic experience started with physician-modified endovascular grafts. Device modifications used the same principles of sizing, design, and implantation applied for manufactured devices. A limitation of the technique was the lack of a reinforced nitinol ring, which is available in manufactured devices. Lack of a reinforced nitinol ring can lead to enlargement of the fenestrations and

Lille-Malmo Experience
Fenestrated Endografts for Juxtarenal AAAs

288 Patients (2002-2012)
Early experience with first 50 patients (~4.7 yr)



	Early experience n=100	Late experience n=188	
Fenestrations	2.7±0.8	3.2±0.8	0.001
2 fen	35	11	
4 fen	7	30	

	Early experience (%) n=100	Late experience (%) n=188	
Fenestrations	2.7±0.8	3.2±0.8	0.001
Fluoroscopy	84 min	65 min	0.05
Contrast volume	254 ml	184 ml	0.05
30-day Mortality (%)	2	2	NS

Fig. 15.8 Results of early experience with fenestrated stent-grafts for juxtarenal abdominal aortic aneurysms in Lille, France and Malmo, Sweden. By permission of Mayo Foundation for Medical Education and Research.

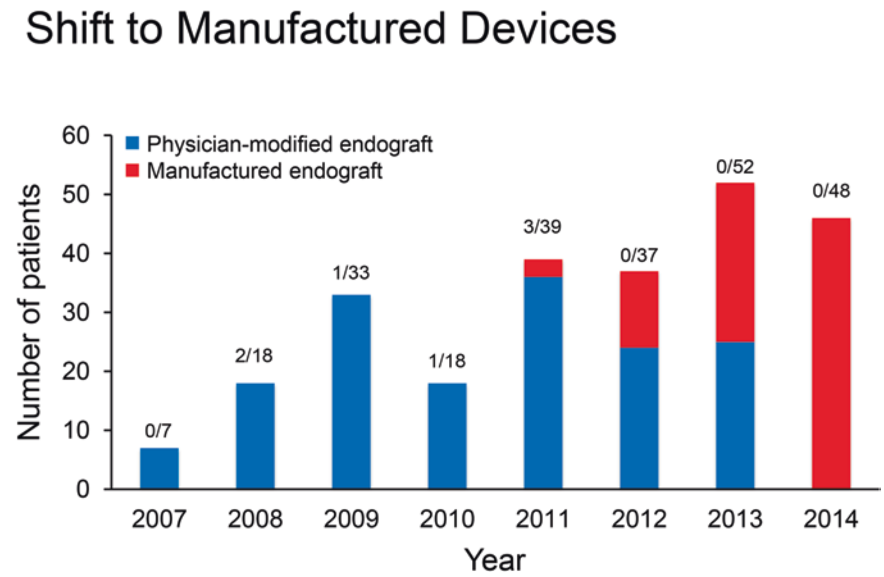


Fig. 15.9 Increasing utilization of manufactured devices has replaced physician-modified fenestrated endografts at the Mayo Clinic. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

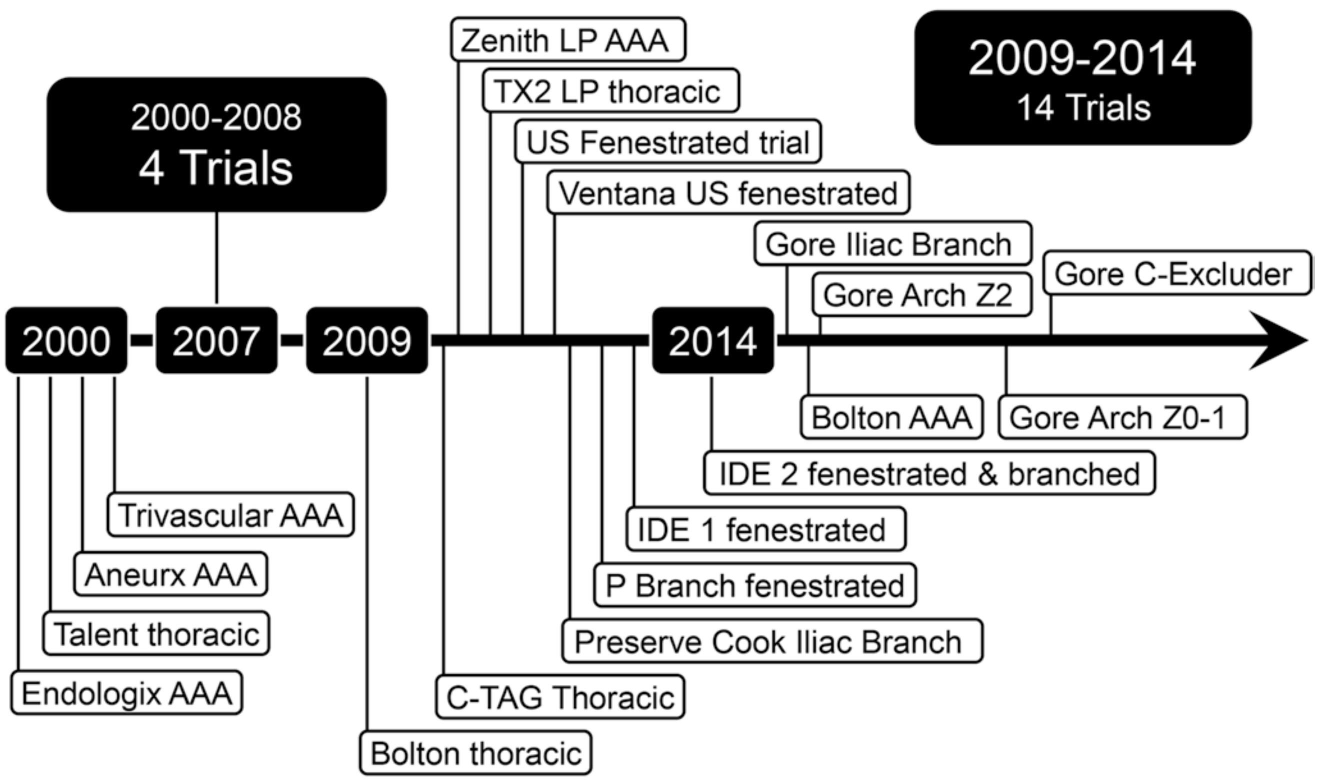
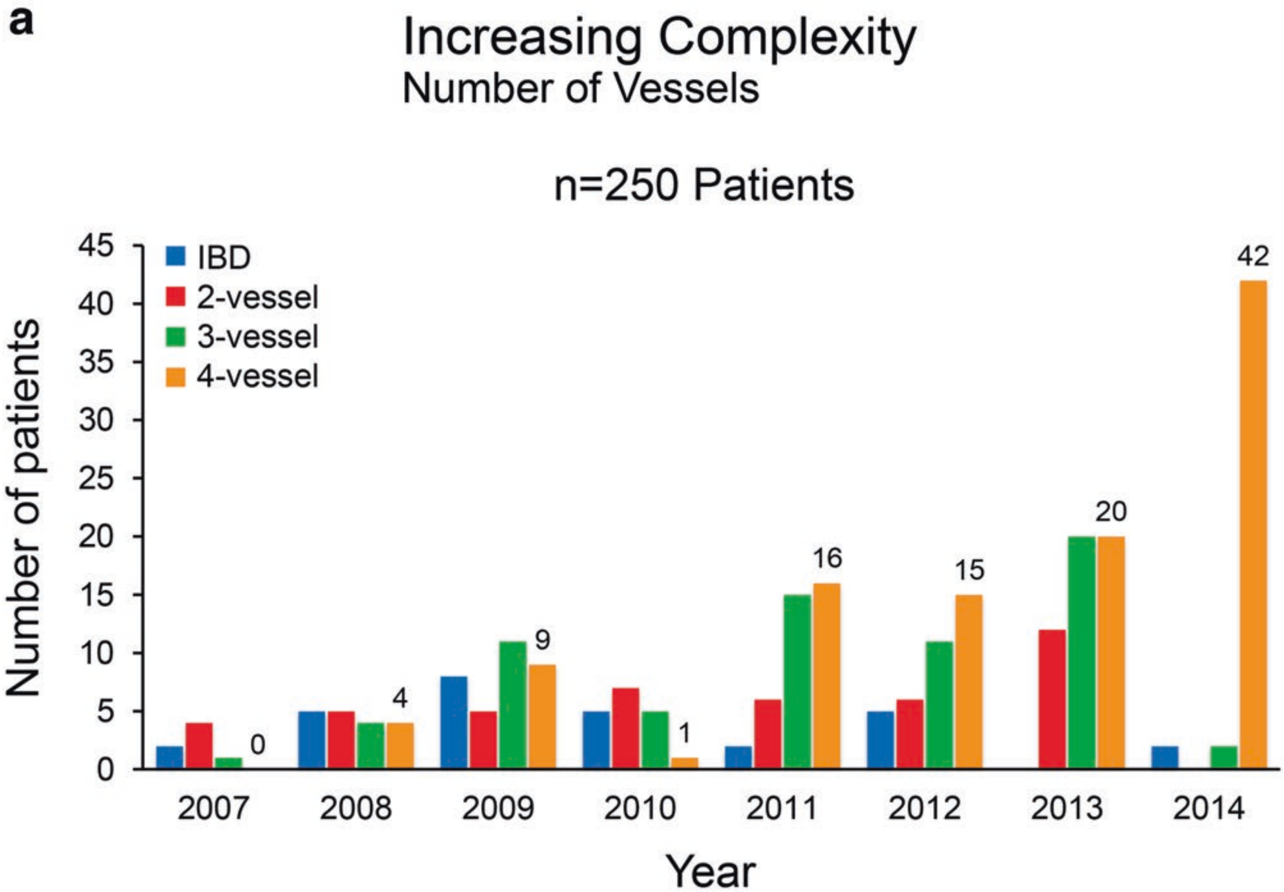


Fig. 15.10 Development of clinical trial section has been possible with collaboration with industry sponsors and engineers. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

poor apposition with alignment stents, predisposing to component separations and type III endoleaks. Other important limitations of PMEGs include the lack of quality control, added cost of using multiple devices, time required for modifications, limited reimbursement, and questionable long-term durability. Therefore, our practice shifted from PMEGs to utilization of manufacture devices (Fig. 15.9, online only) under a prospective physician-sponsored investigational device exemption protocol (IDE). Following the example of Dr. Greenberg, we also developed a robust clinical research program, which currently includes over 20 clinical trials evaluating complex aortic devices (Fig. 15.10). These trials



b Learning Curve

	Patient			P
	1 to 80	81 to 160	161 to 240	
Pararenal (%)	70	74	38	0.01
TAAA (%)	30	26	62	0.01
Vessels (no.)	2.4±1.06	3.04±1.02	3.54±0.75	0.001
2-vessel (%)	50	29	10	0.001
4-vessel (%)	19	41	65	0.001
Fluoroscopy (min)	117±61	84±38	72±23	0.05
Contrast (ml)	237±99	163±73	138±75	0.001
30-day mortality	5 (6%)	2 (3%)	0	0.12

Fig. 15.11 Increasing device complexity at the Mayo Clinic fenestrated-branched program in 250 consecutive cases was associated with more thoracoabdominal aneurysms and more four-vessel designs (**a**) and with decrease in fluoroscopy time and contrast volume (**b**). By permission of Mayo Foundation for Medical Education and Research. All rights reserved

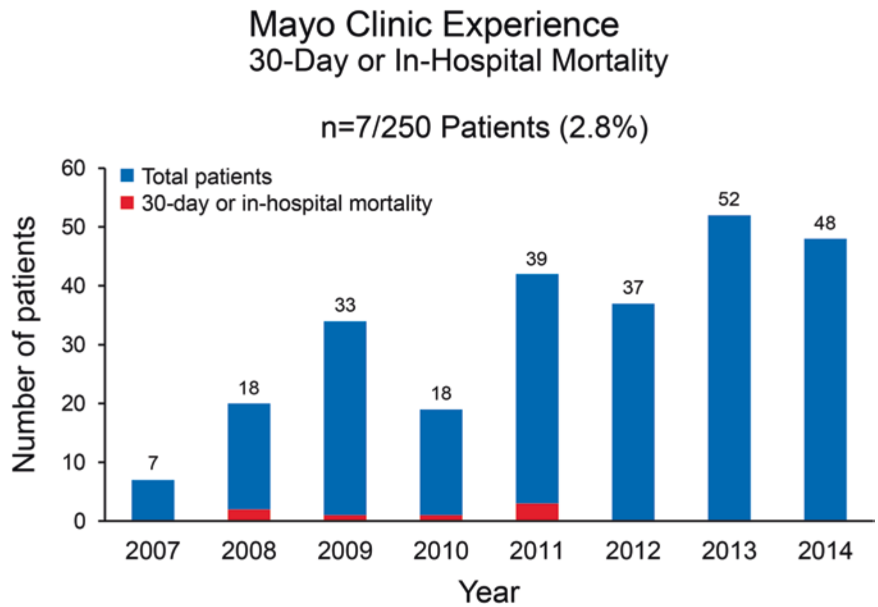


Fig. 15.12 Despite the increase in complexity of repair using more four-vessel fenestrated designs, mortality has decreased over the years. By permission of Mayo Foundation for Medical Education and Research. All rights reserved

also include IDE protocols evaluating outcomes and quality of life measures of patients treated for complex aneurysms, allowing treatment of pararenal and thoracoabdominal aneurysms and dissections with the options of an off-the-shelf multi-branched design (t-branch stent-graft) or custom-made devices with combination of fenestrations and branches. Similar to other centers, we also noted increase in device design complexity (Fig. 15.11) and a trend toward operative mortality in the last few years (Fig. 15.12).

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