

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/semvascsurg

Clinical need, design, and goals for the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis trial

Brajesh K. Lal, MD^a, James F. Meschia, MD^b, and Thomas G. Brott, MD^{b,*}

^aDepartment of Vascular Surgery, University of Maryland School of Medicine, Baltimore, MD

^bDepartment of Neurology, Mayo Clinic, Griffin Building, 3rd Floor, 4500 San Pablo Road, Jacksonville, FL 32224

ARTICLE INFO

ABSTRACT

Prior clinical trials produced evidence-based treatment recommendations for patients with asymptomatic carotid stenosis that may not be appropriate for clinical decision-making today. High-quality patient outcomes data to allow informed decision making regarding the optimal management of high-grade asymptomatic internal carotid artery stenosis is lacking. The results of the Asymptomatic Carotid Atherosclerosis Study were published in 1995 based on a randomized patient enrollment in the 1990s. Outcomes after endarterectomy, stenting, and medical treatment for these patients have all improved in the subsequent 2 decades. Therefore, the time has come to test whether contemporary intensive medical therapy is an acceptable alternative to contemporary endarterectomy or stenting and is the rationale for the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis (CREST-2) trial. This National Institute of Neurological Disorders and Stroke–sponsored prospective, multicenter clinical trial has the investigators, study teams, asymptomatic patients, and robust study design needed to provide these answers. Two randomized clinical trials are planned: carotid revascularization and intensive medical management versus medical management alone in patients with asymptomatic high-grade carotid stenosis randomize in a 1:1 ratio; the other trial will randomize patients in a 1:1 ratio to carotid stenting with embolic protection versus no stenting. ClinicalTrials.gov Identifier: NCT02089217.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Extracranial internal carotid artery atherosclerotic occlusive disease is a common cause of preventable stroke. Estimates of first-time ischemic stroke attributable to carotid artery disease range from 7% to 18% of all incident stroke [1,2]. Multicenter randomized clinical trials (ACAS [Asymptomatic

Carotid Atherosclerosis Study], ACST [10-Year Stroke Prevention After Successful Carotid Endarterectomy for Asymptomatic Stenosis], VACS [Veterans Affairs Cooperative Study]) of carotid endarterectomy (CEA) for stroke prevention in asymptomatic carotid stenosis demonstrated significant benefit of surgery compared to medical therapy [3–5]. However, the absolute risk-reduction favoring surgery tended to be

CREST-2 is funded by the National Institute of Neurological Disorders and Stroke through two U01 awards: U01 NS080168 and U01 NS08016.

*Corresponding author.

E-mail address: brott.thomas@mayo.edu (T.G. Brott).

<http://dx.doi.org/10.1053/j.semvascsurg.2017.04.004>

0895-7967/\$ - see front matter © 2017 Elsevier Inc. All rights reserved.

small. In ACST, at a median follow-up of 9 years, the 5- and 10-year risk of stroke was 6.4% and 13.9% for the CEA group and 10.9% and 17.9% for the medical group, respectively, for an absolute risk reduction of 4.1% at 5 years and 4.6% at 10 years. Since the completion of these trials, medical therapy has improved, carotid artery stenting (CAS) has been introduced as a second method of carotid revascularization, and surgical results of CEA have improved. This has resulted in widespread ambivalence regarding optimal treatment recommendations for the patient with high-grade asymptomatic carotid stenosis [6–9]. The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis (CREST-2) trial aims to ascertain which strategy, revascularization with medical therapy or medical therapy alone, would be the best approach for this large group of patients [10]. It will compare the two revascularization strategies (CEA and CAS) in separate trials, each against medical therapy. In this summary, we provide the rationale, design and goals of CREST-2.

2. Clinical need

2.1. Advances in medical therapy

Medical therapy has advanced since the completion of the earlier trials comparing CEA plus medical therapy to medical therapy alone [11]. Recent data suggest that the stroke rate in medically treated patients with asymptomatic carotid artery stenosis has decreased to $\leq 1\%$ per year [12]. In ACST, the rate of absolute benefit from CEA per year was lower in patients on lipid-lowering therapy (0.6% per year) compared with patients not on lipid-lowering therapy (1.5% per year) [13]. ACST had no explicit targets for low-density lipoprotein, and statin-based intensive targets (eg, low-density lipoprotein < 70 mg/dL) can further reduce the absolute benefit of revascularization. Contemporary medical therapy can be conceptualized as the synergistic combination of antiplatelet therapy (in some cases, dual antiplatelet therapy for a finite period of time), intensive management of elevated blood pressure, dyslipidemia, and diabetes mellitus, as well as targeted lifestyle interventions aimed at tobacco cessation, weight loss, and increasing physical activity. Several physicians have argued that asymptomatic carotid stenosis is a benign disease—if treated medically with contemporary pharmacologic treatments (ie, 21st-century guideline-driven, intensively monitored treatments for hypertension, hyperlipidemia, diabetes, smoking cessation). Perhaps the most pertinent evidence for an improvement in medical therapy comes from two randomized trials comparing treatments for intracranial arterial stenosis. Between 1999 and 2003, the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial randomized 567 patients with symptomatic high-grade intracranial atherosclerotic stenosis to aspirin or warfarin and managed risk factors using standard approaches prevalent during that time [14]. The study observed a 30-day rate of stroke or death of 10.7% and a 1-year rate of the primary end point of 25.7%. Only a decade later (between 2008 and 2011), the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study randomized 451 similar patients to intracranial

stenting or medical therapy [15]. Unlike WASID, medical therapy implemented in this trial was aggressive, guideline-driven, and intensively monitored. For the medical patients in SAMMPRIS, the stroke and death composite outcome (5.8%) and the stroke, myocardial infarction, and death primary composite outcome (12.2%) were both low, about half of what had been achieved in WASID. It is interesting to note that intensive medical therapy was first incorporated into a clinical trial of intracranial stenosis before ever being tested in the far more common condition of cervical carotid stenosis.

2.2. Advances in revascularization therapy

The advent of CAS as an option for carotid revascularization has complicated therapeutic decision-making for asymptomatic carotid stenosis. Randomized controlled trials of CAS compared to CEA have been performed [6,16]. CREST was a randomized trial comparing CEA to CAS in patients with symptomatic ($n = 1,321$) and asymptomatic ($n = 1,181$) carotid artery stenosis. Results based on a mean follow-up of 4 years [6] and follow-up out to 10 years have been reported [8]. In both reports, no significant difference was found for symptomatic and asymptomatic patients in the estimated rates of the primary composite outcome of periprocedural stroke, myocardial infarction, or death and ipsilateral stroke, thereafter. CREST, however, included both symptomatic and asymptomatic patients and did not include a control arm receiving medical therapy alone. Therefore, the question of whether asymptomatic patients require any revascularization remains unanswered.

In addition to the advances made in contemporary intensive medical therapy described here, there have been advances in interventional techniques with improved device technology and operator experience. In CREST, rates for the composite periprocedural outcome of any stroke, myocardial infarction, or death were very low for both treatment groups (4.5% for CEA and 5.2% for CAS) [6]. For the more limited composite outcome of any stroke or death in the first 30 days, rates were even lower; in fact, these rates were the lowest yet achieved in any large, randomized trial of treatment for carotid artery disease. For CEA, the rate was 2.3%, and for CAS, the rate was 4.4%. Importantly, these low rates were accomplished across a broad spectrum of academic and community clinical centers ($n = 117$) located in the United States and Canada. Beyond the trial, favorable secular trends in the safety of CAS have been seen in the Nationwide Inpatient Sample [17]. This may explain the low risk of CAS documented in CREST. There was a simultaneous improvement in outcomes after CEA, likely related to a combination of factors such as improved periprocedural anesthetic care and a broad dissemination of a standardized technique [18]. This is strong evidence that safety for both revascularization procedures continues to improve and has not yet plateaued.

3. Design and goals

CREST-2 trial (ClinicalTrials.gov identifier: NCT02089217)¹⁰ is designed as two parallel randomized trials (Fig. 1). The surgical trial will measure treatment differences between



Fig. 1 – Coordinating centers for Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis.

CEA combined with intensive medical therapy (IMT) versus IMT alone. The stenting trial will measure treatment differences between CAS combined with IMT versus IMT alone. CREST-2 includes adult patients (35 years and older) with $\geq 70\%$ carotid stenosis as measured by duplex ultrasound defined by a peak systolic velocity of at least 230 cm/s plus an end-diastolic velocity of at least 100 cm/s. If the end-diastolic velocity is not ≥ 100 cm/s, patients are eligible for the trial if the internal carotid artery-to-common carotid artery peak systolic velocity ratio is at least 4.0, or computed tomography angiography shows $\geq 70\%$ stenosis, or magnetic resonance angiography shows $\geq 70\%$ stenosis. Patients with $\geq 70\%$ stenosis by North American Symptomatic Carotid Endarterectomy Trial criteria on conventional angiography are also eligible. No stroke or transient ischemic attack can have occurred ipsilateral to the target artery within 180 days before enrollment. Modeled on the SAMMPRIS approach, IMT is centrally directed and protocol-driven to maximize achievement of evidence-based targets for blood pressure and low-density lipoprotein cholesterol. An individualized, centrally managed lifestyle intervention program is implemented to promote tobacco cessation, weight loss, and physical activity. In addition, IMT extends into the perioperative period. Based on experimental and clinical evidence, intensive statin therapy will be used perioperatively (Table 1).

Target recruitment for CREST-2 is 2,480 patients (1,240 in each study; 620 in each treatment group). The primary composite outcome is perioperative stroke or death within 44 days after randomization and any ipsilateral stroke thereafter out to 4 years of follow-up. An important secondary aim is to measure treatment differences between carotid revascularization and medical therapy on cognitive outcomes.

4. Operational details

For the National Institute of Neurological Disorders and Stroke–funded CREST-2, the first step in its long journey

was taken on December 9, 2014, when the first patient was enrolled and randomized by the team at Novant Health Clinical Research, Winston-Salem, NC, under the direction of Dr Donald Heck. While there are many more steps to go before recruitment is completed, we are more confident than ever that this important trial will succeed.

Eighty-nine centers are now actively screening patients for CREST-2 (Fig. 2). In the United States, there are 87 centers across 32 states. In Canada, there are 2 centers across 2 provinces. A total of 54 (60%) of these sites enrolled patients in the CREST trial that compared outcomes of CEA to CAS [8]. Many more centers are looking to come on line. To be a center requires having an established clinical trials infrastructure and a skilled surgeon to perform CEA or a skilled stent operator, preferably both. Certification of these operators requires systematic committee review of detailed procedural records. As demonstrated in the CREST credentialing process, no single statistical rule can replace careful deliberation by the certifying committee [24,25].

Investigators in Canada were major contributors to CREST, which included symptomatic and asymptomatic patients. It is hoped that their contribution to CREST-2 will be as robust, but there are new challenges. Of the 292 patients enrolled at Canadian centers in CREST, 48 (16%) were asymptomatic. There is perhaps less equipoise in Canada than in the United States for revascularizing patients with asymptomatic carotid stenosis. For example, of the 243 patients who underwent carotid stenting at the Foothills Medical Center, Calgary between 1997 and 2007, only 16.1% were asymptomatic [26].

CREST-2 is the first stroke-prevention study to collaborate with the National Institute of Neurological Disorders and Stroke clinical trials network known as StrokeNET. This network consists of 25 regional clinical research centers that are managed by a National Clinical Coordinating Center at the University of Cincinnati. Each regional center partners with several so-called spokes, proximate hospitals that might otherwise lack the resources to participate fully in clinical research. This hub-and-spoke network design has been used

Table 1 – Randomized trials of statin treatment before carotid revascularization.

First author, year	Statin therapy		Revascularization	Outcomes
	Groups	Duration		
Puato, 2010 [19]	AT 80 mg/d v AT 10 mg/d v cholestyramine 8 g/d and sitosterol 2.5 g/d	3 mo	Endarterectomy	Macrophage content reduced proportional to LDL reduction
Cuccurullo, 2006 [20]	Simvastatin 40 mg/d and Step 1 AHA diet v Step 1 diet alone	4 mo	Endarterectomy	Simvastatin inhibited plaque receptor for advanced glycation end products
Martín-Ventura, 2005 [21]	AT 80 mg/d v no statin	1 mo	Endarterectomy	AT reduced macrophage infiltration; activated NF- κ B, COX-2, and MCP-1 expression.
Cipollone, 3002 [22]	Simvastatin 40 mg/d and Step 1 AHA diet v Step 1 diet alone	4 mo	Endarterectomy	Simvastatin reduced macrophages and T-lymphocytes in plaque.
Patti, 2013 [23]	AT reload with 80 mg + 40 mg 12 h before procedure v no reload	12 h	Stenting	AT reload significantly reduced 30-day incidence of stroke/TIA or new postoperative lesions on 24 to 48 h. DWI (18.4% v 35%; $P = .031$).

Abbreviations: AHA, American Heart Association; AT, atorvastatin; DWI, diffusion-weighted imaging; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; NF, nuclear factor; TIA, transient ischemic attack.

successfully in delivery of acute stroke care [27,28], patient education [29], and in the Neurological Emergencies Treatment Trial network [30]. Because CREST-2 was planned well before establishment of StrokeNET, many CREST-2 centers are not part of StrokeNET. The list of potential CREST-2 centers grew out of the CREST experience. Nonetheless, CREST-2 utilizes the central Institutional Review Board (IRB) of StrokeNET, also based at the University of Cincinnati. The central IRB employs reliance agreements with as many centers as will accept this arrangement. In addition to its

mandate of protecting subjects through independent oversight, a central IRB may improve efficiency and consistency of initiation of the trial, processing of amendments, and assuring patient safety. However noble the intent, there is currently scant empirical evidence to support increased trial efficiency through the use of central IRBs [31].

Another important way in which CREST-2 is helping to assure patient safety is the parallel stenting registry known as C2R (ClinicalTrials.gov identifier: NCT02240862). This registry affords stent operators who are being considered for

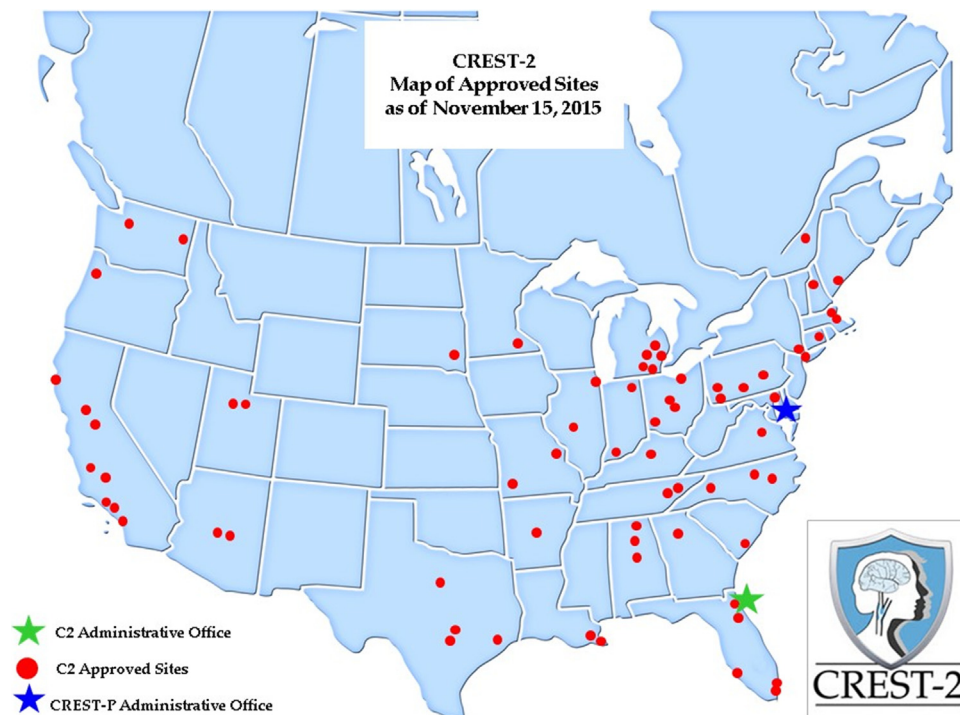


Fig. 2 – Participating centers enrolling patients in Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis (CREST-2).

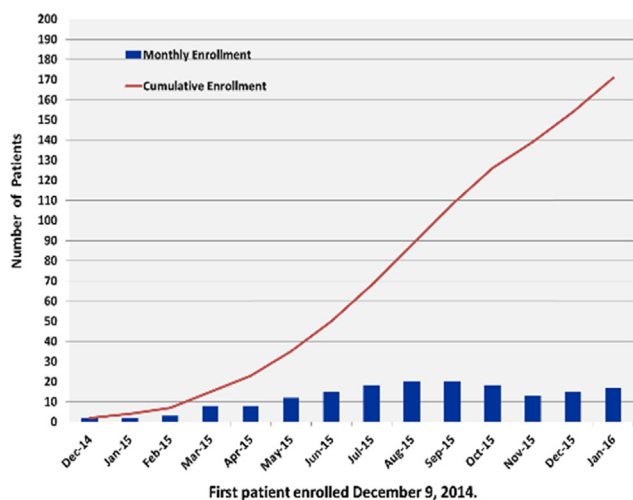


Fig. 3 – Enrollment activity in Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis.

inclusion in CREST-2 the opportunity to gain recent experience under controlled circumstances, with predefined eligibility criteria and short-term outcomes assessments. A remarkable collaboration between the National Institute of Neurological Disorders and Stroke and the Centers for Medicare and Medicaid has made this registry possible. Centers for Medicare and Medicaid reimburses for stenting of C2R cases when performed on Medicare recipients. Registry data will help inform the Interventional Management Committee decisions on approval of individual operators.

CEA has been one of the most rigorously studied procedures, both for primary and secondary stroke prevention. However, CREST-2 faces challenges not encountered by trials like ACAS. In the year 1987, when ACAS began to enroll patients, the burden of proof of efficacy was on CEA and not on the medical management arm. Now that CEA has an evidence-based indication for primary prevention, the burden of proof of efficacy is on the IMT arm of the trial. As has been pointed out, prevention is often celebrated in principle but resisted in practice [32]. As for CAS, an initial burst of enthusiasm for stenting as the less-invasive approach to carotid revascularization has yielded to the sobering fact that it is likely not a lower-risk procedure with regard to periprocedural stroke, even in patients who are at high risk for complications from CEA.

5. Progress

As of April 6, 2016, eighty-nine centers have been approved to randomize, 214 patients have been enrolled, and site selection is ongoing by the CREST-2 Site Selection Committee for up to 150 sites (Fig. 3). The Surgical and Interventional Management Committees have credentialed 263 surgeons and 98 interventionists. An additional 127 interventionists have been approved to submit additional cases via CREST-2 Companion Registry, which provides a Centers for Medicare and Medicaid–reimbursed pathway for full credentialing in CREST-2.

6. Conclusions

Despite the challenges faced by CREST-2, site-selection, operator and stent versus OR selection, site initiation, core facility operations, and data-management functions are now fully operational. It is unlikely that there will be a similar opportunity to demonstrate the risks and benefits of IMT, with or without revascularization, for patients with asymptomatic carotid stenosis in the foreseeable future. We hope that the medical community will appreciate the importance of the trial, and either participate in the trial directly or refer potential patients to one of the participating centers. We owe it to our patients to answer this fundamental question in clinical care.

REFERENCES

- [1] White H, Boden-Albala B, Wang C, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* 2005;111:1327–31.
- [2] Petty GW, Brown RD Jr, Whisnant JP, et al. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke* 1999;30:2513–6.
- [3] Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med* 1993;328:221–7.
- [4] Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;273:1421–8.
- [5] Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363(9420):1491–502.
- [6] Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;363:11–23.
- [7] Spence JD, Naylor AR. Endarterectomy, stenting, or neither for asymptomatic carotid-artery stenosis. *N Engl J Med* 2016;374:1087–8.
- [8] Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med* 2016;374:1021–31.
- [9] Rosenfield K, Matsumura JS, Chaturvedi S, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med* 2016;374:1011–20.
- [10] Lal BK, Meschia JF, Brott TG. CREST-2: Guiding treatments for asymptomatic carotid disease (September 2013). *Endovasc Today* 2013;1:73–6.
- [11] Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke* 2009;40:e573–83.
- [12] Marquardt L, Geraghty OC, Mehta Z, et al. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke* 2010;41:e11–7.
- [13] Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010;376(9746):1074–84.
- [14] Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;352:1305–16.

- [15] Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365:993–1003.
- [16] Gurm HS, Yadav JS, Fayad P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;358:1572–9.
- [17] Choi JH, Pile-Spellman J, Brisman JL. US nationwide trends in carotid revascularization: hospital outcome and predictors of outcome from 1998 to 2007. *Acta Neurol Scand* 2014;129:85–93.
- [18] Munster AB, Franchini AJ, Qureshi MI, et al. Temporal trends in safety of carotid endarterectomy in asymptomatic patients: systematic review. *Neurology* 2015;85:365–72.
- [19] Puato M, Faggin E, Rattazzi M, et al. Atorvastatin reduces macrophage accumulation in atherosclerotic plaques: a comparison of a nonstatin-based regimen in patients undergoing carotid endarterectomy. *Stroke* 2010;41:1163–8.
- [20] Cuccurullo C, Iezzi A, Fazia ML, et al. Suppression of RAGE as a basis of simvastatin-dependent plaque stabilization in type 2 diabetes. *Arterioscler Thromb Vasc Biol* 2006;26:2716–23.
- [21] Martín-Ventura JL, Blanco-Colio LM, Gómez-Hernández A, et al. Intensive treatment with atorvastatin reduces inflammation in mononuclear cells and human atherosclerotic lesions in one month. *Stroke* 2005;36:1796–800.
- [22] Cipollone F, Fazia M, Iezzi A, et al. Suppression of the functionally coupled cyclooxygenase-2/prostaglandin E synthase as a basis of simvastatin-dependent plaque stabilization in humans. *Circulation* 2003;107:1479–85.
- [23] Patti G, Tomai F, Melfi R, et al. Strategies of clopidogrel load and atorvastatin reload to prevent ischemic cerebral events in patients undergoing protected carotid stenting. Results of the randomized ARMYDA-9 CAROTID (Clopidogrel and Atorvastatin Treatment During Carotid Artery Stenting. *J Am Coll Cardiol* 2013;61:1379–87.
- [24] Hopkins LN, Roubin GS, Chakhtoura EY, et al. The Carotid Revascularization Endarterectomy versus Stenting Trial: credentialing of interventionalists and final results of lead-in phase. *J Stroke Cerebrovasc Dis* 2010;19:153–62.
- [25] Howard G, Voeks JH, Meschia JF, et al. Picking the good apples: statistics versus good judgment in choosing stent operators for a multicenter clinical trial. *Stroke* 2014;45:3325–9.
- [26] Shobha N, Almekhlafi MA, Pandya A, et al. Carotid stenting in asymptomatic carotid stenosis: the Calgary experience. *Can J Neurol Sci* 2010;37:568–70.
- [27] Switzer JA, Demaerschalk BM, Xie J, et al. Cost-effectiveness of hub-and-spoke telestroke networks for the management of acute ischemic stroke from the hospitals' perspectives. *Circ Cardiovasc Qual Outcomes* 2013;6:18–26.
- [28] Demaerschalk BM, Switzer JA, Xie J, et al. Cost utility of hub-and-spoke telestroke networks from societal perspective. *Am J Manag Care* 2013;19:976–85.
- [29] Rogers H, Turner E, Thompson G, et al. Hub-and-spoke model for a 5-day structured patient education programme for people with type 1 diabetes. *Diabet Med* 2009;26:915–20.
- [30] Ginsberg MD, Palesch YY, Hill MD, et al. High-dose albumin treatment for acute ischaemic stroke (ALIAS) Part 2: a randomised, double-blind, phase 3, placebo-controlled trial. *Lancet Neurol* 2013;12:1049–58.
- [31] Check DK, Weinfurt KP, Dombeck CB, et al. Use of central institutional review boards for multicenter clinical trials in the United States: a review of the literature. *Clin Trials* 2013;10:560–7.
- [32] Fineberg HV. The paradox of disease prevention: celebrated in principle, resisted in practice. *JAMA* 2013;310:85–90.