SECTION 1.0

INTRODUCTION AND BACKGROUND
1.1 REVIEW OF LITERATURE

This section includes a brief overview of carotid artery disease, treatment options for carotid artery disease, including best medical therapy, carotid endarterectomy (CEA) and carotid artery stenting (CAS), as well as published data including treatment history and outcomes.

1.1.1 Stroke and Carotid Artery Disease

According to Heart Disease and Stroke Statistics 2009 Update (Lloyd-Jones, Adams et al. 2010) from the American Heart Association (AHA), there are 610,000 new and 185,000 recurrent strokes each year. Stroke is the third most common cause of mortality in the United States. The lifetime risk of stroke is one in five for women and one in six for men (Seshadri, Beiser et al. 2006). According to the Centers for Disease Control and Prevention (CDC), strokes are the leading cause of long-term disability (CDC 2001).

Of all strokes, 87% are ischemic. Carotid artery disease accounts for 20% of ischemic strokes (Lloyd-Jones, Adams et al. 2010). By AHA definition, “atherosclerotic lesions are considered advanced by histological criteria when accumulations of lipid, cells, and matrix components, including minerals, are associated with structural disorganization, repair, and thickening of the intima, as well as deformity of the arterial wall”. A building-up of an atherosclerotic lesion in a carotid artery causes carotid artery disease and carotid (artery) stenosis. Carotid stenosis occurs most frequently in the internal carotid artery (ICA) and bifurcation of the common carotid artery (De Fabritiis, Conti et al. 2002). ICA stenosis is a common condition in the general population over 65 years old and more frequent at the age between 75-85 than at a younger age (Gorelick and Alter 2002).

The primary mechanisms of carotid artery disease-related ischemic stroke are occlusion of the artery and emboli in the cerebral vasculature, caused by atherosclerotic debris or thrombotic materials from carotid artery lesions. The primary goal in the treatment of carotid artery disease is long-term stroke prevention.

1.1.2 Medical Treatment and CEA for Carotid Artery Disease

Historically, medical therapy has been the first option in treating carotid artery disease and thus identified its role in the prevention of strokes. In the last few years, dual antiplatelet therapy with aspirin and another antiplatelet agent such as clopidogrel or ticlopidine has become standard of care for patients with cardiovascular disease especially after stenting. Section 1.1.2.1 summarizes the published articles of medical therapy through mid 2010.

After clinical trials evaluating the outcome of CEA compared to medical therapy, CEA has been proven effective in reducing the risk of stroke. CEA is now considered the gold standard of care for patient populations with carotid stenosis since the completion of the
landmark trials. NASCET, a landmark trial of 2226 patients showing the safety of endarterectomy in patients with moderate or severe stenosis, was published in 1991 (NASCET Collaborators 1991) and ACAS, a trial which was demonstrated that the addition of carotid endarterectomy to aggressive medical management reduced the incidence of cerebral infarction in patients with asymptomatic carotid artery stenosis, was published in 1995 (Executive Committee for ACAS 1995). Section 1.1.2.2 summarizes the published data of CEA treatment.

CAS is an emerging procedure and technology. The clinical outcomes in the high surgical risk population have consistently shown to be acceptable in comparison to CEA. As seen in the data collected and subjects treated, CAS has become an alternative treatment for subjects at high risk for CEA. Section 1.1.2.3 summarizes the published data regarding high risk CEA.

All three treatment options have proved equally important in treating subjects with carotid artery disease. Medical therapy is mostly used to stabilize plaque, while CEA is performed to surgically remove plaque. CAS has provided a less invasive treatment compared to CEA to revascularize narrowed or occluded arteries.

The outcomes of published clinical trials comparing CAS and CEA treatments are presented in Section 1.1.3.

1.1.2.1 Medical Therapy-Medication

Antiplatelet medications are used in prevention of strokes and have been studied intensively during the past two decades. The statin drug family and some antihypertensives have also shown some effects in reducing risk for stroke. Since there has been no clear evidence that an oral anticoagulant, for example warfarin, decreases the incidence of carotid artery disease-related strokes, the efficacy of this drug family in stroke prevention will not be reviewed. This maybe due to the fact that the status of the ICA stenosis was not commonly evaluated during the medical therapy trial.

Aspirin Mono-Antiplatelet Therapy

Aspirin, the oldest and most widely used antiplatelet agent, was evaluated by three major randomized clinical trials (RCT) regarding its efficacy in stroke prevention. In 1991, the data from the first RCT, Swedish Aspirin Low-Dose Trial (SALT) were published in Lancet (The SALT Collaborative Group 1991). The trial randomized 1,360 subjects with any symptoms of transient ischemic attack (TIA), amaurosis fugax, minor ischemic stroke and retinal artery occlusion within the previous three months to either an aspirin (75 mg/day) or a placebo group in 15 clinical centers in Sweden. After a follow-up with a median of 2.6 years, the trial revealed that the risk of primary outcome events (stroke or death) was 20.4% in subjects receiving aspirin vs. 25% in those receiving placebos ($p = 0.02$), with an 18% relative risk reduction (RRR) demonstrating benefit in stroke prevention.
In the same year, a trial conducted in The Netherlands, the Dutch TIA study was published in the New England Journal of Medicine (The Dutch TIA Trial Study Group 1991). In this trial, 3,131 subjects with a recent history of stroke or TIA were randomized to either a 30 mg/day aspirin or a 283 mg/day aspirin regimen and followed for a mean of 2.6 years. The study found the composite outcome of vascular death, nonfatal stroke, or nonfatal acute myocardial infarction (MI) was 14.7% in subjects who received 30 mg/day aspirin and 15.2% in those who received 283 mg/day aspirin, revealing no statistically significant difference between high and low dose aspirin regimens. Subjects on high dose aspirin regimen had 3.3% major bleeding complications while those subjects on the lower dose regimen had 2.6%. A post hoc analysis of data from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial published in the Annals of Internal Medicine in March 2009, revealed that an aspirin regimen of 100 mg/day or more did not provide more benefit than 75 or 81 mg/day aspirin (Steinhubl, Bhatt et al. 2009).

The last RCT evaluating aspirin efficacy in stroke prevention was the United Kingdom Transient Ischemic Attack Aspirin Study (UK-TIA) and the results were published in 1991 (Farrell, Godwin et al. 1991). UK-TIA enrolled 2,435 subjects with recent TIA or minor ischemic strokes. Subjects were randomized to one of three arms: (1) a placebo, (2) a 300 mg/day aspirin and (3) a 1200 mg/day aspirin. After a mean follow-up of approximately 4 years, the study showed a 15% RRR in the primary composite endpoint of vascular death, nonfatal strokes, or nonfatal acute MI between the 300 mg/day aspirin and placebo. There was no evidence of statistically significant differences between aspirin arms in the composite endpoint; however, the high dose aspirin arm had a higher rate of upper gastrointestinal symptoms and bleeding episodes.

The aforementioned trials demonstrate that aspirin in stroke prevention requires only a low dose; increasing the aspirin dose only increases the risk of adverse events, but not efficacy. At its lower dose, aspirin is a safe and inexpensive agent. Overall, aspirin monotherapy has only a 15-18% RRR for stroke, and in higher doses it causes noteworthy gastrointestinal discomfort and bleeding. In addition, there is evidence that some subjects developed a resistance to aspirin (Eikelboom, Hirsh et al. 2002). These findings promoted efforts in finding other antiplatelet agents or a combination of antiplatelet agents as an alternative to aspirin.

Non-Aspirin Mono-Antiplatelet Therapy

In 1989, ticlopidine, a thienopyridine drug family became the first non-aspirin antiplatelet agent evaluated for stroke prevention in a multicenter RCT (Gent, Blakely et al. 1989). The Canadian American Ticlopidine Study (CATS) evaluated the efficacy of the antiplatelet agent ticlopidine in the prevention of recurrent stroke. The study randomized 1,053 subjects with a history of recent atherothombotic or lacunar stroke to either a placebo or ticlopidine (2 × 250 mg/day) arm. The mean follow-up period was 2 years, the study results showed the composite outcome of stroke, acute MI, or vascular death was 10.8% in subjects in the ticlopidine group and 15.3 % in those in the placebo group.
The Ticlopidine Aspirin Stroke Study (TASS) results were published in the New England Journal of Medicine in 1989 (Hass, Easton et al. 1989). The trial randomized 3,069 subjects with a history of TIA or minor stroke to ticlopidine (500 mg/day) or aspirin (2 × 650 mg/day) in 56 North American centers. After a mean follow-up of 2 years, the risk of fatal and nonfatal stroke was 10% in the ticlopidine group and 13% in the aspirin group \((p = 0.024, \text{RRR } 21\%)\). The incidence of the composite endpoint of stroke or death by any cause was only slightly lower in the ticlopidine group than in the aspirin group \((17\% \text{ vs. } 19\%, p = 0.048, \text{RRR } 12\%)\). The adverse event rate was higher in ticlopidine recipients; however, less than 1% of ticlopidine recipients experienced severe neutropenia, a known adverse effect of ticlopidine.

In 2003 (Gorelick, Richardson et al. 2003), the results of another trial that studied a small population of African Americans, the African American Antiplatelet Stroke Prevention Study (AAASPS) were published. The AAASPS trial randomized 1,809 African American men and women with a history of noncardioembolic stroke to ticlopidine (500 mg/day) or aspirin (650 mg/day). The primary composite outcome variable of recurrent stroke, acute MI, or vascular death at 2 years was 14.7% in the ticlopidine group and 12.3% in the aspirin group \((\text{RRR } 1.22\%)\), which was not statistically significant. The study was terminated prematurely because analysis of the initial results revealed a near-zero probability of showing superiority of ticlopidine over aspirin.

Clopidogrel, another antiplatelet drug derived from thienopyridine, was first studied through a large population RCT, the Clopidogrel versus Aspirin in Patients at Risk of Recurrent Ischemic Events (CAPRIE). The study results were published in 1996 (CAPRIE Steering Committee 1996). The trial enrolled 19,185 subjects who had a recent ischemic stroke, recent MI or symptomatic peripheral arterial disease in 384 clinical centers in 16 countries. Subjects were randomized to an aspirin group (325 mg/day) or a clopidogrel group (75 mg/day). The primary efficacy endpoint was the composite of ischemic stroke, MI, or vascular death. After a mean follow-up of 1.91 years, the primary endpoint rate was 5.32% in the clopidogrel group and 5.83% in the aspirin group \((p = 0.043)\) with a 0.51% absolute risk reduction \((\text{ARR})\) and an 8.7% RRR. However, the stroke recurrence between the groups was not statistically significant \((p = 0.27)\). The overall safety profile of clopidogrel observed was similar to that of medium-dose aspirin.

**Dual-Antiplatelet Therapy**

Several RCTs were conducted to evaluate the efficacy of two combined antiplatelet agents in stroke prevention. The rationale behind the combination antiplatelet therapy was a postulation that blocking platelet aggregation through multiple mechanisms would increase efficacy of antiplatelet agents in recurrent ischemic stroke prevention.

In 1990, the results from the European Stroke Prevention Study (ESPS) were published
(ESPS Group 1990). It was the first large trial aimed at determining whether the combination regimen of dipyridamole and aspirin could prevent recurrent stroke. The ESPS-1 trial randomized 2,500 subjects who had experienced a stroke or TIA within the past 3 months to either a combination group of aspirin (330 mg/day) and immediate-release dipyridamole (3 × 75 mg/day) or a placebo group in 12 clinical sites in six countries. After a mean follow-up period of 2 years, the rate of stroke or death from any cause was 15.2% in the combination group and 22.6% in the placebo group \((p < 0.001)\), which yielded a 7.4% ARR and 33.5% RRR, respectively. The incidence of stroke, including fatal and nonfatal stroke, was 9.1% in the combination group versus 14.7% in the placebo \((p < 0.001)\), a 38.1% RRR.

Since the ESPS trial only answered the question regarding the combination therapy of dipyridamole and aspirin versus placebo but not the combination therapy versus aspirin monotherapy, ESPS-2 was carried out in 60 clinical sites in 13 countries after the completion of ESPS-1. The ESPS-2 trial randomly assigned 6,602 subjects with a history of TIA or ischemic stroke in the past 3 months into one of the four arms: (1) aspirin alone (25 mg/day), (2) extended-release dipyridamole (ER-DB, 2 × 200 mg/day) alone, (3) aspirin (25 mg/day) plus ER-DB (2 × 200 mg/day), or (4) placebo. The primary endpoints were stroke, death, and composite of stroke or death at a mandatory 2-year follow-up for all subjects. The results were published in 1996 (Diener, Cunha et al. 1996). The risk of stroke or death was 15.1% in the placebo arm versus 12.5% in the aspirin arm \((p = 0.013, \text{RRR} 18\%)\), 12.3% in the ER-DB alone arm \((p = 0.039, \text{RRR} 16\%)\), and 9.5% in the combination arm \((p < 0.001, \text{RRR} 37\%)\). However, the incidence of all-site bleeding and gastrointestinal bleeding was significantly higher in subjects who received aspirin than in those who received placebo or only ER-DB.

An additional effort to explore the efficacy in ER-DB plus aspirin was the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT). The trial results were published in 2006 (Halkes, van Gijn et al. 2006). ESPRIT aimed at evaluating whether aspirin plus ER-DB would be more effective than aspirin alone at right doses in the prevention of recurrent vascular events. The trial randomized 2,763 subjects who had a TIA or minor stroke of presumed arterial origin within the previous 6 months to an aspirin (30 - 325 mg/day) plus placebo group, or an aspirin (30 - 325 mg/day) plus ER-DB (2 × 200 mg/day) group in multiple clinical sites in 16 countries. The primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication. After a mean follow-up period of 3.5 years, primary outcome events occurred in 13% (173/1363) of subjects treated with aspirin plus ER-DB compared with 16% (216/1376) of subjects treated with aspirin plus placebo (hazard ratio 0.80, 95% CI 0.66–0.98) in the intent-to-treat population, which yielded a 20% RRR in favor of aspirin plus ER-DB.

Another RCT investigating a different combination of antiplatelets was the Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) trial. It was designed to determine whether aspirin in combination with clopidogrel would further reduce the risk of recurrent ischemic vascular events in high-risk subjects after TIA or ischemic stroke. The trial enrolled 7,599 subjects with a history of ischemic stroke or
TIA within the past 3 months, plus one additional cardiovascular risk factor (i.e., previous stroke, previous MI, angina, diabetes mellitus, or symptomatic peripheral artery disease) in 507 medical centers in Asia, North America and Europe. Subjects were randomized to a clopidogrel (75 mg/day) alone group or a clopidogrel (75 mg/day) plus aspirin (75 mg/day) group. The trial results were published in 2004 (Diener, Bogousslavsky et al. 2004). There was no evidence of a statistically significant difference between the two groups in the rate of a composite of ischemic stroke, MI, vascular death, or re-hospitalization for acute ischemia (including re-hospitalization for TIA, angina pectoris, or worsening of peripheral arterial disease). The life-threatening bleeding event rate was 2.6% in subjects who received clopidogrel plus aspirin versus 1.3% in those subjects ($p < 0.0001$) who received clopidogrel alone.

Similarly, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) was another trial that sought greater protection against cardiovascular events through the combination of clopidogrel with aspirin. In 2006, the trial results were published (Bhatt, Fox et al. 2006). CHARISMA enrolled 15,603 subjects with coronary artery disease, cardiovascular disease, symptomatic peripheral arterial disease or multiple risk factors for cardiovascular disease at 768 clinical sites in 32 countries. Subjects were randomized to a clopidogrel (75 mg/day) plus aspirin arm (75 - 162 mg/day) or an aspirin only arm (75 - 162 mg/day). After a mean follow-up period of 2.3 years, no statistically significant difference was found between clopidogrel plus aspirin (6.8%) and aspirin alone (7.3%) in the rate of MI, stroke, or cardiovascular related death.

The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial was the largest among all antiplatelet therapy studies. The results were published in the New England Journal of Medicine (Sacco, Diener et al. 2008). The ESPS-2 and ESPRIT trials had shown that the combination of aspirin and ER-DB is better than aspirin alone for prevention of recurrent stroke, as well as prevention of stroke, MI and death from vascular causes without increasing the risk of major bleeding. In a head-to-head comparison, the PRoFESS trial was designed to evaluate the efficacy between the two antiplatelet regimens: ER-DB plus aspirin and clopidogrel. A total of 20,332 subjects were randomized to either ER-DB (200 mg/day) plus aspirin (25 mg/day) group or a clopidogrel only group (75 mg/day) in 695 centers in 35 countries. After a mean follow-up period of 2.5-years, the 2-by-2 factorial trial revealed the recurrent stroke rate in ER-DB plus aspirin group was 9% and also 9% in the clopidogrel group, showing no statistically significant difference in stroke prevention between the two regimens. However, subjects who received ER-DB plus aspirin experienced more major hemorrhagic events (4.1%) than those who received clopidogrel (3.6%, hazard ratio, 1.15; 95% CI, 1.00 to 1.32).

Medical Therapy Other Antiplatelets

Two classes of medications other than antiplatelets were also studied through RCT. One class is the statin family, a 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitor,
which lowers total cholesterol and low-density lipoprotein (LDL). The other class is a group of drugs that control blood pressure through the renin-angiotensin-aldosterone system either by angiotensin-converting enzyme (ACE) inhibition or by an angiotensin II receptor blocker (also known as angiotensin II receptor antagonist).

In 2006, the Reduction in Cholesterol Levels (SPARCL) investigators published the study results (Amarenco, Bogousslavsky et al. 2006). The SPARCL trial randomized 4,731 subjects with a history of stroke or TIA and elevated LDL to an 80 mg/day atorvastatin (a statin family drug) group or a placebo group at 205 clinical centers. The primary endpoint was a first non-fatal or fatal stroke. After a median follow-up period of 4.9 years, the 5-year risk of stroke was 11.2% in atorvastatin recipients versus 13.1% in placebo recipients, with a 2% ARR and a 14.5% RRR ($p = 0.03$).

A post hoc analysis of SPARCL explored whether atorvastatin had a greater impact on recurrent stroke reduction in subjects with carotid artery stenosis compared to subjects without stenosis of the carotid artery. The carotid artery stenosis was reported as present, absent or unknown at the time when the subject was randomized to the study. If the degree of stenosis was reported, the diagnosis was not reviewed or adjudicated. The post hoc analysis showed that the 5-year risk of stroke was 11.2% in atorvastatin recipients and 16.1% in placebo recipients (a 30% relative reduction of stroke, $p = 0.0197$) among the subjects who had reported carotid artery stenosis (average of 51%). However, the analysis also showed that there was no statistically significant difference between the atorvastatin and placebo recipients in stroke reduction among those subjects who did not have reported carotid stenosis (11.2% vs. 12.3%, $p = 0.2413$) (Sillesen, Amarenco et al. 2008).

Another trial, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) released results in 2008 (Ridker, Danielson et al. 2008). The trial enrolled 17,802 subjects without history of a stroke or TIA and randomized subjects to either a rosuvastatin regimen (20 mg/day) or a placebo regimen. After a median follow-up of 1.9 years, a subgroup analysis revealed that all strokes were 0.34 (64 / 8901) and 0.18 (33/8901) per 100 person-years of follow-up in the placebo and rosuvastatin groups respectively ($p < 0.002$), further supporting statin efficacy in prevention of strokes.

The first published ACE inhibitor RCT study was the Heart Outcomes Prevention Evaluation (HOPE) in 2000 (Yusuf, Sleight et al. 2000). The HOPE trial enrolled 9,297 subjects who had vascular disease or diabetes, plus one cardiovascular disease risk factor in 281 clinical centers in North America, South America and Europe. Subjects were randomized to either a Ramipril (an ACE inhibitor) or a placebo group. The mean follow-up period was 5 years, the study revealed that the recipients of Ramipril had a 3.4% risk of stroke in comparison to the recipients of placebo who had a 4% ($p < 0.001$) risk of stroke, showing a 1.5% ARR and 31% RRR.

In 2003, the results of Perindopril Protection against Recurrent Stroke Study (PROGRESS) were published (Chalmers and MacMahon 2003) The trial enrolled 6,105
subjects with a history of stroke or TIA in 172 clinical centers in Asia and Europe. All subjects were randomized to either a placebo arm or a perindopril (4 mg/day) plus indapamide (a diuretic drug) arm at the choice of treating physicians. After 4 years of follow-up, treatment recipients had a 10% risk of a stroke compared with the placebo recipients who had a 14% risk of stroke ($p < 0.0001$, RRR 28%).

Conclusion

In summary, medical therapy has its role in the prevention of strokes. Low dose aspirin has repeatedly shown to have about a 15-18% RRR in strokes as compared to placebo. Presently, no other solo antiplatelet agent has better efficacy than aspirin monotherapy. Aspirin plus ER-DB is the only antiplatelet combination therapy that has a better outcome than aspirin monotherapy. However, the incidence of serious adverse events is higher in combination therapy.

Published in 2008 (Albers, Amarenco et al. 2008) the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommends antiplatelet therapy to reduce risk of a recurrent stroke in subjects with noncardioembolic stroke or TIA. Aspirin (50 - 325 mg/day), aspirin plus ER-DB (25 - 200 mg twice daily), and clopidogrel (75 mg/day) are all acceptable options. In addition, published in 2008 (Hobson, Mackey et al. 2008) the Clinical Practice Guidelines of the Society for Vascular Surgery recommends only medical therapy for the symptomatic subjects with less than 50% carotid stenosis and asymptomatic subjects with less than 60% carotid stenosis. The guidelines released to the public in 2006 (Sacco, Adams et al. 2006) from the AHA/American Stroke Association (ASA) Council on Stroke recommends aspirin (75 – 325 mg/day) for prevention of recurrent stroke in subjects with history of carotid artery disease-related ischemic stroke or TIA.

1.1.2.2 Carotid Endarterectomy (CEA)

CEA is a surgical procedure performed by usually either a neurosurgeon or a vascular surgeon. For this procedure, the subject is placed in a supine position on the operating table with special positioning of the head and the neck. Following appropriate anesthesia, a skin incision is made at the level of the carotid bifurcation. The carotid artery on the side of treatment is then cross-clamped to stop blood flow for an average of 18 minutes (Malek, Malek et al. 2005) that allows for arteriotomy and removal of the plaque. For subjects who may be intolerant to cross clamping, a shunt may be inserted to reduce ischemia time.

CEA, since it first demonstrated feasibility in 1954, has experienced continuing controversy for many years regarding its role in the management of carotid artery disease due to a high peri-operative stroke rate. A community center-based study has shown that the CEA peri-operative stroke rate dropped from 8.6% to 5.1% between 1980 and 1984 (Brott, Labutta et al. 1986). Within the same period, the peri-procedural stroke or death rate fell from 9.5% to 6.5%. By the end of the 20th century, after almost three decades of
studies and practice, CEA became the standard of care for invasive management of symptomatic and asymptomatic subjects with severe carotid artery stenosis.

Two randomized multicenter clinical trials, the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), assessed the risks and benefits of CEA in comparison to a control of medical therapy alone in symptomatic subjects. The ECST trial results were published in 1991 and 1998 (Warlow 1991; ECST Collaborative Group 1998). The trial enrolled 3,024 subjects who had recently suffered a stroke and had carotid stenosis as evidenced by angiography; subjects were randomized to either a CEA group or a control group in which CEA was to be avoided for as long as possible. Subjects in both arms received what was judged to be the best medical treatment. After an average 6.1-year follow-up, the stroke and death rate was 14.9% in the CEA group and 26.5% in the control group at 3 years, which corresponds to an 11.6% ARR (or a 44% RRR). The 30-day peri-procedural stroke and death rate was 7.0% for the CEA subjects. The ECST investigators also found that the estimated risk of stroke and death at 2-3 years increased with the severity of stenosis, especially when the stenosis was between 70-80%, supporting a conclusion that the benefit of reduced long-term risk in subjects with 80% stenosis outweighed the risk of surgical stroke.

NASCET enrolled 2,885 symptomatic subjects under 80 years old and randomized them to either a CEA group or a best medical treatment arm (defined as low dose aspirin) in 50 clinical centers in the United States and Canada. Symptomatic carotid stenosis was defined as those subjects who had carotid stenosis and a non-disabling stroke or TIA within 180 days prior to enrollment into the study. The primary outcome event was all stroke ipsilateral to the treated stenosis. The results of NASCET were published in 1991 and 1998 (NASCET Collaborators 1991; Barnett, Taylor et al. 1998). For subjects with a 50-69% carotid stenosis, the rate of stroke and death in the 30-day peri-procedural period was 6.7%. The 2-year ipsilateral stroke rate was 14.6% in the medical group versus 9.3% in the CEA group, yielding an ARR of 5.3% or 36% RRR. The 5-year ipsilateral stroke risk for the subjects with the same grade of stenosis was 22.2% in the medical group but 15.7% in the CEA group, with a 6.5% ARR or 29% RRR ($p < 0.05$). In 659 subjects with a 70-99% carotid stenosis with an average follow-up duration of 18 months, a cumulative risk of any ipsilateral stroke rate at 2 years was 26% for the medical subjects and 9% for the surgical subjects, an ARR 17% or 65% RRR ($p < 0.001$). The enrollment of subjects with high-grade stenosis was stopped prematurely because the efficacy of CEA was shown.

After the ECST and NASCET trials revealed the role of CEA in reducing the risk of stroke in the symptomatic subject population, three RCTs were conducted in the asymptomatic subject population who had ICA stenosis: the Veterans Affairs Study (VAS), the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST).

In 1993, VAS results were published (Hobson, Weiss et al. 1993). The trial enrolled 444 men, who had 50-99% angiographic carotid stenosis at 11 Veterans Affairs Medical
Centers in the United States. All subjects were randomly assigned to either a CEA plus aspirin regimen (2 × 650 mg/day), or an aspirin alone regimen (2 × 650 mg/day). Subjects treated with CEA plus aspirin had an 8% overall ipsilateral neurological event rate, compared with 20.6% for the aspirin alone group (p < 0.001) at the 4-year follow-up. However, these neurological events included TIA, which does not cause any lasting clinical deficit. The analysis of the results, excluding TIA, revealed that the ipsilateral stroke rates were 4.7% for the CEA group and 9.4% for the medical group, which was not statistically significant, but clinically relevant.

ACAS, the second RCT in asymptomatic subjects under 80 years old published in 1995 (Executive Committee for ACAS 1995), enrolled 1,662 subjects with > 60% carotid stenosis, defined by ultrasound and confirmed by angiography. Subjects from 38 clinical centers in the United States were randomized to either a CEA plus aspirin arm (325 mg/day) or an aspirin alone arm (325 mg/day). The risk of stroke or death in CEA is 2.3% within 30 days. All enrolled subjects in both arms were also under risk factor reduction management, which included counseling and interventions for hypertension, obesity, hyperlipidemia, diabetes mellitus, tobacco abuse, inactive lifestyle, use of estrogen compounds, and polycythemia. After a median follow-up of 2.7 years, with 9% completing 5-year follow-up, the estimated 5-year ipsilateral stroke rate and any peri-operative stroke or death over 5 years was 5.1% in the CEA group and 11% in the aspirin management group with a 5.9% ARR (p = 0.004) or a 53% RRR.

In 2004, the results from ACST, the last multicenter RCT in an asymptomatic patient population were published (Halliday, Mansfield et al. 2004). The trial enrolled 3,120 subjects who had a minimum 60% carotid stenosis measured by ultrasound. Subjects from 126 medical centers in 30 countries were randomized to either an immediate CEA arm or a deferred CEA medical arm (without CEA, unless symptoms occurred). The risk of stroke or death within 30 days of CEA was 3.1%. The net 5-year risk of all strokes and peri-operative events was only 6.4% in the immediate CEA group and 11% in the deferred medical group. The 5-year stroke risk excluding peri-operative events was 3.8% in CEA versus 11% in the deferred medical group, a 7.2% ARR (p < 0.0001) or a 60% RRR.

1.1.2.3 High Risk for CEA

High risk factors for CEA subjects are classified into the following categories:

Age:

Age as one of the high risk factors was proven by several previous studies (Varghese and Norman 2004). A review of CEA covering 10 states in the United States revealed that subjects at age 75 years or older had higher risk of mortality than those who were at 65 years or younger (Saleh and Hannan 2004). Subjects over 80 years old were excluded from the NASCET (NASCET Collaborators 1991) and ACAS 1.0 almost done. (Executive Committee for ACAS 1995) trials because of their risk profile.
Contralateral carotid artery occlusion:

Contralateral carotid artery occlusion, a condition where the non-operative carotid vessel has no antegrade flow distal to the occlusion, also puts the subjects at greater risk for neurologic complications during CEA due to reduced cerebral blood flow during the clamping of the operative blood vessel. In the NASCET trial, there was a 14.3% stroke and death rate at 30 days in the subjects who had an occluded contralateral carotid artery and a severely stenosed ipsilateral carotid artery (NASCET Collaborators 1991). In addition, the ACAS investigators also found that the asymptomatic subjects with contralateral occlusion had a 2% absolute increased risk (95% CI, 29.3% to 5.2%) in peri-procedural complications in comparison to those subjects without contralateral occlusion (Executive Committee for ACAS 1995).

Unfavorable anatomy:

Increased risk of peri-procedural complications may occur due to severe potential anastomotic challenges such as spinal immobility, contralateral laryngeal nerve paralysis, and any medical condition that requires a tracheostomy. Diethrich (Diethrich 1996) found that the risk of CEA complications was increased by the following: CEA of a lesion residing above the bifurcation would more likely cause nerve damage, post-radiation in the neck area results in the loss of landmarks and causes tissue to become tough, “leather-like”, and nerve adhesion to the surrounding tissue from previous CEA.

Medical and Surgical Comorbidities:

Many medical and surgical comorbidities are considered high risk factors for CEA and are listed in the exclusion criteria in the NASCET and ACAS trials. These medical or surgical conditions include: coronary artery bypass graft (CABG) surgery, congestive heart failure (CHF), coronary artery disease with unstable angina, recent (< 6 months) or evolving MI, a recent major surgery (< 1 month) or synchronous operation, atrial fibrillation, valvular disease, renal failure, pulmonary failure and liver failure.

Coyle et al (Coyle, Gray et al. 1995) reported a 26.2% stroke and death rate at 30 days in 110 subjects who had undergone a concomitant CABG with CEA. In a group of asymptomatic carotid stenosis subjects who had a concurrent CABG and CEA, the rate of post-procedural stroke and death was 18.7% (Goldstein, Samsa et al. 1998) in comparison to 2.1% in those who only had CEA. In a review paper (McCory, Goldstein et al. 1993) the rate of post-operative stroke, death and MI was 40% in subjects who had CABG prior to CEA versus 6.5% in those who had only CEA. There was no difference in outcomes of death, stroke and MI when the CABG was staged or synchronous with CEA. Naylor et al (Naylor, Cuffe et al. 2003) found that 11.5% subjects who had concurrent CEA/CABG procedures suffered peri-operative stroke, death, or MI versus 10.2% of those who had staged procedures. Wong et al (Wong, Findlay et al. 1997) conducted a regional review on the performance of CEA and found that subjects who had CHF exhibited a 25% post-procedural stroke and death rate and a 50% cardiac...
complications rate versus only 4% and 7%, respectively, in subjects who did not have CHF.

Tu et al, (Tu, Wang et al. 2003) reviewed the medical records of 6,038 subjects who underwent CEA in Ontario, Canada. They identified five medical history factors with significantly elevated odds ratios (OR) for peri-operative stroke or death: TIA or stroke (OR 1.75), atrial fibrillation (OR 1.89), contralateral carotid occlusion (OR 1.72), CHF (OR 1.80), and diabetes (OR 1.28). Greenstein et al (Greenstein, Chassin et al. 2007) also reported that subjects with cardiac complications including MI, unstable angina, pulmonary edema, or ventricular tachyarrhythmia exhibited a 4 to 5 fold increased odd of stroke or combined risk of death and stroke.

1.1.3 Clinical Trials of CAS versus CEA

CAS is a percutaneous endovascular procedure. Generally, a delivery catheter is advanced into a common carotid artery through a femoral artery incision and a stent is deployed to the lesion location.

Under the current AHA/ASA guidelines (Sacco, Adams et al. 2006) for CEA, the strongest indication for symptomatic subjects to have CEA is high grade stenosis (≥ 70%); a good indication for asymptomatic subjects is high grade stenosis (> 75%). The Clinical Practice Guidelines of the Society for Vascular Surgery recommend CEA plus medical therapy for symptomatic subjects with > 50% carotid stenosis and for asymptomatic subjects with ≥ 60% carotid stenosis (Hobson, Mackey et al. 2008). In addition, the AHA guideline recommended that the indication for symptomatic subjects to be treated with CEA are those with < 6% risk of death and stroke and for asymptomatic subjects with < 3% risk at 30 days post-procedure (Moore, Barnett et al. 1995). These Guidelines, established based on CEA, have been used to evaluate outcomes of CAS procedures.

1.1.3.1 CAS Clinical Trials of Subjects at High Risk for CEA

Several clinical trials were conducted to study CAS in subjects at high risk for adverse event from CEA. These studies demonstrated the safety and effectiveness of CAS as a stroke prevention therapy in subjects with multiple clinical and anatomic co-morbidities. Carotid stent systems became commercially available in the United States as early as 2004, following approval of premarket notifications for treatment of high risk subjects.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was the first multicenter, prospective RCT comparing CAS and CEA along with a distal protection device. Its data were published in 2004 (Yadav, Wholey et al. 2004). The study randomized 334 subjects who had > 50% carotid stenosis and were symptomatic or > 80% carotid stenosis and were asymptomatic, to either a CAS or CEA arm in 29 United States sites from 2000 to 2002. Enrolled subjects had a history of clinically significant cardiac diseases, severe pulmonary diseases,
octogenarians, contralateral carotid occlusions, contralateral cranial nerve injuries, previous radical neck surgery or radiation, restenosis following previous CEA. The primary endpoint for this study was the cumulative incidence of death, stroke, or MI within the 30-day peri-procedural period and death or ipsilateral stroke between 31 days and 1 year. The study results revealed the cumulative outcome of 12.2% for CAS and 20.1% for CEA, demonstrating CAS with embolic protection device (EPD) was not inferior to CEA ($p = 0.004$). In addition, the 30-day stroke and death rate was 4.7% for CAS and 5.3% for CEA; there was no statistically significant difference between the two arms, further supporting the conclusion that CAS with EPD is not inferior to CEA.

Several single-arm clinical trials aimed at evaluating safety and efficacy of CAS were conducted in the past decade. All trials were multicenter studies, enrolling subjects who were at high risk for CEA and used an objective performance criterion (OPC), intending to show non-inferiority of CAS with a direct surgical comparator. An OPC was derived from historical high-CEA-risk subject outcomes in clinical trials and adjusted based on the actual subject mix in an actual trial. The results from those single-arm trials are part of our knowledge base in terms of understanding the safety and efficacy aspects of CAS in the high risk for CEA population.

A single-arm, multicenter, prospective, clinical trial, the Acculink for Revascularization of Carotids in High-Risk Patients (ARCHeR) was conducted. This study was designed to determine whether CAS with embolic protection was a safe and effective alternative to CEA in subjects at high risk for adverse events from CEA. The ARCHeR Study results, published in 2006 [Gray et al, 2006], evaluated the Acculink or RX Acculink Carotid Stent System when used with the Accunet or RX Accunet Embolic Protection System. These were the first approved and cleared devices in the United States in 2004. ARCHeR is discussed in Section 1.3.1.3.

Several post-approval clinical trials, also known as post-market surveillance studies were conducted to satisfy a condition of approval of carotid stent systems from the FDA. The first one is the Carotid RX Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) sponsored by Abbott Vascular. CAPTURE was intended to evaluate clinical outcomes associated with the use of approved devices by community-based physicians with a variety of specialties and levels of experience in CAS, and to identify device-related adverse events. The results [Gray et al, 2007] were published in 2007. CAPTURE is discussed in Section 1.3.2.2.

In 2009 (Massop, Dave et al. 2009) the results of the first 2,001 subjects from another post-approval trial were published. The SAPHIRE Worldwide registry (SAPHIRE WW) is designed to evaluate CAS with distal emboli protection in the treatment of carotid artery disease. SAPHIRE WW is an on-going multicenter, prospective, post-approval clinical trial currently being conducted in 350 clinical sites in the United States and Canada. The study population of the trial is subjects with $\geq 50\%$ symptomatic or $\geq 80\%$ asymptomatic carotid stenosis and at high risk for CEA. The primary endpoint of the study is a composite MAE rate including death, MI and stroke at 30 days post-procedure. At 30-day follow-up from the first 2,001 subjects, the MAE rate was 4.4% for
the overall population.

In March 2009, the results of two recent post-approval studies were published (Gray, Chaturvedi et al. 2009). The Emboshield and Xact Post-Approval Carotid Stent Trial (EXACT) was a post-approval clinical trial using the Xact Carotid Stent System with the Emboshield Embolic Protection System. CAPTURE 2 was a post-approval trial using the RX Acculink Carotid Stent System when used with the RX Accunet Embolic Protection System. A total of 2,145 EXACT and 6,361 CAPTURE 2 subjects, with either ≥ 50% symptomatic or ≥ 80% asymptomatic carotid stenosis and was at high risk for CEA have been enrolled at 280 United States sites. The result of the CAPTURE 2 study is discussed in Section 1.3.2.3.

A subset analysis in EXACT and CAPTURE 2, showed the combined death and stroke rate at 30-day was 5.3% (95% CI: 3.6%, 7.4%) for symptomatic subjects and 2.9% (95% CI: 2.4%, 3.4%) for asymptomatic subjects meeting the AHA guidelines defining that the combined 30-day death and stroke rate is acceptable at < 3% for asymptomatic and < 6% for symptomatic subjects.

1.1.3.2 CAS Clinical Trial of Subjects at Standard Risk for CEA

As of 2010, 6 clinical trials have evaluated the efficacy of CAS in subjects at standard risk for CEA. The first one was a multicenter RCT, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). The CAVATAS trial was conducted at 24 centers in Europe, Australia, and Canada in both symptomatic and asymptomatic subjects at standard risk for CEA. The primary outcome for this trial was disabling stroke and death at 30 days. At the beginning, the trial aimed at comparing CEA and angioplasty. Stenting was rolled into the trial later when it became available. A total of 253 subjects were enrolled in the CEA arm and 251 in the endovascular arm. For subjects treated successfully in endovascular arm, 158 (74%) were treated with balloon angioplasty and 55 (26%) with CAS, but without use of an embolic protection device. Revealed in a 2001 publication (CAVATAS investigators 2001), the rate of death or disabling stroke at 30 days was 9.9% for CEA subjects and 10% for endovascular subjects, showing no statistically significant difference between the two arms. The 1-year stroke or death rate further demonstrated no significant difference between CEA (13.4%) and endovascular treatments (14.3%).

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was a multicenter RCT aiming to demonstrate non-inferiority of CAS to CEA in subjects at standard risk for CEA. The primary endpoint was defined as the rate of ipsilateral stroke or death from randomization to 30 days post-procedure. A 2.5% margin of non-inferiority was determined based on the power calculation of 1,900 subjects. As revealed in the publication in 2006 (Ringleb, Allenberg et al. 2006) the SPACE steering committee stopped the trial due to lack of financial resources to continue enrollment. As a result, SPACE actually enrolled 1,200 subjects with ≥ 50% symptomatic carotid artery stenosis at 35 centers in Germany, Austria, and
Switzerland. The trial randomly assigned 605 subjects to the CAS arm and 595 subjects to the CEA arm. The rate of ipsilateral stroke or death from randomization to 30 days post-procedure was 6.84% for CAS and 6.34% for CEA ($p = 0.09$). The primary endpoint rates were comparable, although the results could not prove non-inferiority of CAS to CEA due to early termination.

The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was a RCT designed to demonstrate the non-inferiority of CAS. Its results were published in 2006 (Mas, Chatellier et al. 2006). The EVA-3S trial studied symptomatic patients with ≥ 60% carotid stenosis at standard risk for CEA versus CAS in 20 clinical centers in France. The primary endpoint was 30-day stroke or death. The trial was prematurely stopped due to safety concerns and lack of efficacy after the enrollment of 527 of the intended 872 patients. The use of embolic protection was not mandatory at the early stage of the trial. A subgroup analysis showed that subjects who underwent CAS without embolic protection experienced a 25% stroke or death rate at 30 days, which warranted the suspension of the enrollment and a protocol amendment, making use of an embolic protection device mandatory by the EVA-3S safety committee. The 30-day stroke or death rate was 3.9% for CEA versus 9.6% for CAS ($p = 0.01$). The 6-month stroke or death rate was 6.1% for CEA and 11.7% for CAS ($p = 0.02$) and the study was terminated for safety concerns at this stage. Although it appeared that CEA had a better outcome, critics commented that this outcome was the result of having the best CEA surgeons versus CAS operators with “little or no experience” and “severely limited training” (Setacci and Cremonesi 2007; Beckett and Gaines 2008).

The Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) trial was the only non-randomized clinical trial conducted with standard risk subjects for CEA. CaRESS was designed to evaluate the safety and efficacy of CAS with embolic protection in comparison to CEA. In this concurrently controlled trial, the choice of the treatment was solely made by subjects and their physicians. All subjects enrolled in CaRESS had either a > 50% symptomatic carotid stenosis or a > 75% asymptomatic carotid stenosis, and were at standard risk for CEA. As revealed by published results in 2003 and 2005 (CARESS Steering Committee 2003; CARESS Steering Committee 2005), 397 subjects were enrolled in the CEA arm (N = 254) and the CAS arm (N = 143) at 14 United States sites. The subject baseline demographics including risk levels for a stroke were similar in both arms, except that more subjects with a restenotic artery after CEA received CAS rather than CEA. The primary endpoints were death and stroke at 30 days, a composite 1-year endpoint including death, stroke or MI at 30 days and death or stroke from 31 days to 1 year. The 30-day death and stroke rate was 2.1% for CAS and 3.6% for CEA (CARESS Steering Committee 2005). At 1 year, the composite endpoint rate was 13.6% for CEA and 10.0% for CAS. Both primary endpoints showed no statistically significant difference between CAS and CEA. The study investigators concluded that the 30-day and 1-year risk of death, stroke, or MI with CAS is equivalent to that of CEA in both symptomatic and asymptomatic subjects. The overall morbidity and mortality were similar to the results of CEA in NASCET and ACAS.

Recently, the investigators of the International Carotid Stenting Study (ICSS), a
multicenter, international, RCT with blinded adjudication of outcomes comparing stenting with endarterectomy for recently symptomatic carotid artery stenosis, published short-term results (120 days) of the trial (Ederle, Dobson et al. 2010). The primary endpoint for ICSS is the 3-year rate of disabling stroke in any territory. The trial enrolled 1713 non-octogenarian subjects with symptomatic carotid artery stenosis and at standard risk for CEA. All subjects were randomized to CAS and CEA at a 1:1 ratio. While the primary endpoint will be evaluated at 3 years, the 120-day interim analysis showed a rate of stroke, death or procedural MI (DSMI) was 8.5% in CAS arm and 5.2% in CEA arm ($p = 0.006$). Also, the 30-day rate of death and stroke was 7.4% in the CAS group and 3.4% in the CEA group ($p = 0.0004$).

The result of the NIH analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was published in NEJM (Brott, Hobson et al. 2010). The primary endpoint for the NIH analysis was a composite of any stroke, MI, or death within 30 days, or ipsilateral stroke during follow-up. With an average of 2.5-year follow-up, the estimated primary endpoint at 4 years was 7.2% in the CAS arm and 6.8% in the CEA arm ($p = 0.51$), demonstrating there was no statistically significant difference in DSMI at 30 days plus ipsilateral stroke to 4 years between CAS and CEA. The CREST analysis revealed a higher 30-day rate of stroke (4.1%) in the CAS arm than in the CEA arm (2.3%) that was statistically significant; conversely, the CEA arm had a higher 30-day rate of MI (2.3%) than the CAS arm (1.1%) that was also statistically significant. In addition, in the symptomatic population, the 30-day death and stroke rate was 6.0% in CAS and 3.2% in CEA; in the asymptomatic population, the 30-day death and stroke rate was 2.5% and 1.4% in CAS and CEA respectively. Both the CAS and CEA arms met the AHA threshold of 6% death and stroke rate for symptomatic and 3% for asymptomatic subjects.

The outcome of trials evaluating carotid stenting in both the high and standard risk populations have improved over time.

1.1.4 Summary

Each of the three options, medical therapy, CEA and CAS, plays its unique role in the prevention of stroke. Medical therapy as a non-invasive approach has its advantage, as it does not require a surgical procedure or hospitalization. To date, aspirin monotherapy is still the best medical therapy because it requires a low dose, is less expensive and is relatively safe. The role of medical therapy in stroke prevention is relatively small, with an average of 15-18% RRR for aspirin. Some antplatelet combination therapies show enhanced efficacy (20-37% RRR) but also displays increased serious adverse events. In addition, for most subjects who participated in medical therapy clinical trials, the status of ICA stenosis was not reported. The ACAS and ACST trials have demonstrated that CEA plus best medical therapy has a 53% and a 60% RRR over best medical therapy, respectively. Unless other risk factors warrant caution, subjects with carotid stenosis are currently recommended for CEA under AHA guidelines. Furthermore, medical therapies, such as antplatelet, lipid control, and angiotensin-related hypertension control
agents, have become general medical practice in the patient population who has related risk factors.

Clinical trials evaluated the outcome of CEA as compared to medical therapy. CEA has been proven effective in reducing the risk of stroke. CEA is now considered the gold standard of care for patient populations with carotid stenosis.

CAS is an emerging procedure and technology. The clinical outcomes in the high surgical risk population have consistently shown to be acceptable in comparison to CEA. As seen in the data collected and subjects treated, CAS has become an alternative treatment for subjects at high risk for CEA. CREST is the first randomized trial comparing CAS and CEA in standard surgical risk population. The published results from the NIH analysis indicated that there was no statistical difference in 4 year outcome between CAS and CEA.

Over the past 20 years, subjects have benefited from all three therapies.
1.2 SUMMARY OF INVESTIGATIONAL DEVICES

CREST was conducted using four devices, the Acculink and RX Acculink Carotid Stent Systems and the Accunet and RX Accunet Embolic Protection Systems.

The Acculink and RX Acculink Carotid Stent Systems are comprised of two primary components, the Acculink Carotid Stent and either an over-the-wire or rapid exchange delivery system. These system components are described in Sections 1.2.1 and 1.2.2. Complete device descriptions can be found in Section 4.0 of the PMA Supplement.

The Acculink Carotid Stent System was initially used in the randomized phase of CREST in December 2000. The Acculink Carotid Stent System was replaced by the RX Acculink Carotid Stent System in April 2004.

The Accunet and RX Accunet Embolic Protection Systems are also comprised of two primary components, a Guide Wire with Filter Basket constrained by a Delivery Sheath and a Recovery System. Section 1.2.3 provides summary descriptions of the Accunet and RX Accunet Embolic Protection Systems. Complete device descriptions can be found in Section 4.0 of the PMA Supplement.

The Accunet Embolic Protection System was introduced into the randomized phase of CREST in October 2001. The Accunet Embolic Protection System was replaced by the RX Accunet Embolic Protection System in April 2004; a second Recovery Catheter introduced in September 2005 is now included with the RX Accunet Embolic Protection System.

1.2.1 Acculink Carotid Stent

The Acculink Carotid Stent is a self-expanding nitinol stent composed of nickel-titanium that is super-elastic at body temperature. The stent design is based on a series of serpentine rings that are connected at 3 locations around the circumference. The connections are aligned along a common longitudinal axis and are positioned 120 degrees from each other. The serpentine rings are designed to nest within adjacent rings and minimize the space between stent struts. The same Acculink Carotid Stent is used for both the Acculink and RX Acculink Carotid Stent Systems. The Acculink Carotid Stent is available in diameters of 5, 6, 7, 8, 9, and 10 mm and lengths of 20, 30, and 40 mm in a straight configuration; a tapered configuration is available in diameters from 6-8 mm and 7-10 mm, each available in lengths of 30 and 40 mm.

The stent is manufactured to be stable at its desired final diameter. The stent is implanted into a target vessel, which is smaller than the stent diameter, so that the stent applies a force to the vessel to keep it open. Tables 1.2-1 and 1.2-2 recommend appropriate straight and tapered stent diameters for compatible carotid reference vessel diameters.
## Table 1.2-1. Acculink Carotid Stent - Straight Stent Diameters

<table>
<thead>
<tr>
<th>Unconstrained Stent Diameter (mm)</th>
<th>Stent Length (mm)</th>
<th>Reference Vessel Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>20, 30, 40</td>
<td>3.6 - 4.5</td>
</tr>
<tr>
<td>6.0</td>
<td>20, 30, 40</td>
<td>4.3 - 5.4</td>
</tr>
<tr>
<td>7.0</td>
<td>20, 30, 40</td>
<td>5.0 - 6.4</td>
</tr>
<tr>
<td>8.0</td>
<td>20, 30, 40</td>
<td>5.7 - 7.3</td>
</tr>
<tr>
<td>9.0</td>
<td>20, 30, 40</td>
<td>6.4 - 8.2</td>
</tr>
<tr>
<td>10.0</td>
<td>20, 30, 40</td>
<td>7.1 - 9.2</td>
</tr>
</tbody>
</table>

## Table 1.2-2. Acculink Carotid Stent - Tapered Stent Diameters

<table>
<thead>
<tr>
<th>Unconstrained Stent Diameter (mm)</th>
<th>Stent Length (mm)</th>
<th>ICA Reference Vessel Diameter (mm)</th>
<th>CCA Reference Vessel Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0 to 8.0 Taper</td>
<td>30, 40</td>
<td>4.3 - 5.4</td>
<td>5.7 - 7.3</td>
</tr>
<tr>
<td>7.0 to 10.0 Taper</td>
<td>30, 40</td>
<td>5.0 - 6.4</td>
<td>7.1 - 9.1</td>
</tr>
</tbody>
</table>

### 1.2.2 Acculink and RX Acculink Carotid Stent Systems

The Acculink and RX Acculink Carotid Stent Systems are comprised of two components, a Stent Delivery System and the Acculink Stent (described in Section 1.2.1 above). The same Acculink Stent is delivered by both the Acculink and RX Acculink Stent Delivery Systems, described in the following two sections.

#### 1.2.2.1 Acculink Stent Delivery System

The Acculink Stent Delivery System is a single-use device that uses a sheath to mechanically constrain the Acculink Carotid Stent at a small diameter for delivery to the treatment site. The system is inserted into the vasculature through a guide catheter or sheath, and tracked over a 0.014” guide wire in a coaxial, over-the-wire (OTW) configuration. Radiopaque markers, located on the delivery system at the proximal and distal ends of the stent, aid in accurate placement of the stent in the lesion. With the handle in a locked position, retracting the pullback handle withdraws the sheath and deploys the Acculink Stent. The stent expands at body temperature, from the distal to the proximal end, as the sheath is retracted.

#### 1.2.2.2 RX Acculink Stent Delivery System

The RX Acculink Stent Delivery System, a rapid-exchange (RX) version of the Acculink Stent Delivery System, also uses a sheath to mechanically constrain the same Acculink
Stent. The system is inserted into the vasculature through a guide catheter or sheath and is tracked over a 0.014” guide wire that passes through the coaxial, distal 22cm of the system. All other features of the System are the same as for the Acculink Carotid Stent System.

The change from an OTW to RX platform was made to accommodate user preference and enhance device usability. The RX platform allows for use of a shorter guide wire (300 cm for the OTW system and 190 cm for the RX system) and enables device use by a single operator. The device eliminates the need for exchange wires, allows for easier guide wire manipulation, and potentially decreases the amount of time required for a carotid stenting procedure. Thus, the design of the RX Acculink System leverages the design of the Acculink System with modifications to the delivery system. Both delivery systems deploy the identical stent with equivalent deployment characteristics.

1.2.3 Accunet and RX Accunet Embolic Protection Systems

The Accunet Embolic Protection System is an over-the-wire (OTW) or rapid exchange (RX) filtration type, embolic protection device, filtering distal to the intervention site. The Accunet guide wire is a single use, steerable 0.014” guide wire system, 300 cm in length, which includes a nickel-titanium filter basket at the distal end for trapping embolic material during endovascular procedures. Radiopaque markers are located on the guide wire, filter basket, and delivery sheath to aid in device positioning. The Accunet Embolic Protection Systems were cleared under K042218.
1.3 HISTORY OF ACCULINK AND ACCUNET USE IN CLINICAL TRIALS

The safety and effectiveness of the Acculink and RX Acculink Carotid Stent Systems when used with the Accunet and RX Accunet Embolic Protection Systems have been evaluated in a series of feasibility, pivotal, and post-approval studies conducted over a span of 10 years since 1999. These studies have focused on the use of these devices in symptomatic and asymptomatic subjects who are at high surgical risk. CREST is the first IDE trial to evaluate the device in standard surgical risk population.

The results of the Abbott Vascular feasibility and pivotal studies in the high risk subject population, described in Section 1.3.1, were submitted to the FDA in an original premarket application (P040012) in March 2004.

FDA granted approval of the Acculink and RX Acculink used with the Accunet and RX Accunet Systems in August 2004 for treatment of patients at high risk for adverse events from CEA who require carotid revascularization and meet the criteria outlined below.

- Patients with neurological symptoms and $\geq 50\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and with $\geq 80\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram, AND
- Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.

The long-term outcome for patients participating in the feasibility and pivotal trials described in Section 1.3.1 was evaluated following approval of PMA P040012. Subjects consenting to an additional two years of follow-up were enrolled in the ARCHer Long-Term Follow-Up Study that is described in Section 1.3.2.1.

Additional post-approval studies have been conducted that serve to confirm the results of the pivotal clinical trials for the Acculink and RX Acculink Carotid Stent Systems when used with the Accunet and RX Accunet Embolic Protection Systems. Sections 1.3.2.2 and 1.3.2.3 summarize the design and results of the CAPTURE (N = 4331) and CAPTURE 2 (N = 6361) post-approval studies.

These devices were also evaluated in a large post-approval study, the CHOICE Study, in which a total of 6872 subjects have been enrolled and treated. In the CHOICE Study, physicians could select the Abbott Vascular RX Acculink Carotid System used with the RX Accunet Embolic Protection System or the Abbott Vascular Emboshield NAV\textsuperscript{6} Embolic Protection System. The physician could also choose to use the Abbott Vascular Xact Carotid Stent System with either the Emboshield or Emboshield NAV\textsuperscript{6} Embolic Protection System. This study is presented and discussed in Section 1.3.2.4.

The results from these studies have provided data supporting the safe and effective use of the Abbott Vascular carotid stent systems when used with their compatible embolic...
protection systems in the treatment of subjects with carotid artery disease who are at high risk for CEA. The successful use of these devices in a high risk population suggests the potential benefit to subjects who are at standard risk for CEA.

Use of the Acculink and RX Acculink Carotid Stent Systems and the Accunet and RX Accunet Embolic Protection Systems is currently being evaluated in a standard risk population that is the subject of this PMA Supplement. CREST is a randomized trial prospectively comparing the results of carotid artery stenting (CAS) to CEA. The history and evolution of CREST is presented in Section 1.3.3.

1.3.1 Acculink/Accunet Feasibility and Pivotal Clinical Studies Overview

1.3.1.1 Acculink Feasibility Study

The Acculink Feasibility Study (IDE G980303) was a prospective, non-randomized, multicenter feasibility study to assess the safety of the Acculink Carotid Stent System in the treatment of moderate to high risk surgical subjects with internal carotid artery (ICA) stenosis. The Acculink Feasibility Study was conducted prior to the introduction of the use of embolic protection in CAS procedures.

A total of 50 subjects were enrolled at 7 investigational sites in the United States between August 5, 1999 and December 28, 1999. The key enrollment criteria was moderate to high risk surgical subjects who were symptomatic (history of a TIA or stroke within 180 days before enrollment) with \( \geq 50\% \) ICA stenosis or asymptomatic with \( \geq 70\% \) ICA stenosis.

Clinical follow-up was conducted at the following intervals: 2 weeks (laboratory work only for subjects taking ticlopidine), 1 month, 3 months, 6 months, and 12 months. The primary endpoints were acute success (device, procedure and clinical) and the composite of death, stroke and MI (DSMI) at 30 days. Device success was defined as the attainment of a final result, < 30\% residual stenosis covering an area no longer than the original lesion length, using the Acculink Carotid Stent System. Procedure success was defined as attainment of a final result, < 30\% residual stenosis covering an area no longer than the original lesion length, using the Acculink Carotid Stent System and any adjunctive device. Clinical success was defined as procedure success without DSMI, emergency CEA, or percutaneous transluminal angioplasty (PTA)/thrombolysis of the target vessel within 7 days of the procedure. In addition, longer term outcome data including ipsilateral stroke, target lesion revascularization (TLR) and symptomatic restenosis at 3, 6, and 12 months were also collected. Access sites complications requiring treatment were also evaluated as a secondary endpoint. The Clinical Events Committee (CEC) adjudicated all major endpoints.

The results are descriptive in nature. The rates of device success, procedure success and clinical success were 95.9\%, 95.9\% and 85.7\%, respectively. The 30-day combined rate of DSMI was 10\%, including two deaths, one major and two minor strokes, and no
myocardial infarctions. No ipsilateral stroke (disabling and non-disabling) after 30 days, TLR or symptomatic restenosis (TIA or stroke plus ≥ 50% stenosis) were reported in the study period. Three subjects experienced access site complications that resolved following treatment.

In conclusion, the observed 30-day endpoint rate of 10% for DSMI was acceptable. The 30-day results of the feasibility study indicated that the Accunet Carotid Stent System could be safely implanted in subjects of moderate to high surgical risk.

1.3.1.2 Accunet Feasibility Study

The Accunet Feasibility Study (IDE G000114) was a prospective, non-randomized, multicenter feasibility study to assess the safety of the Accunet Embolic Protection System with the Accunet Carotid Stent System in the treatment of subjects with lesions in the internal carotid artery (ICA).

A total of 51 subjects were enrolled at 9 sites in the United States between July 11, 2000 and December 7, 2000. Subjects were eligible for participation in the study if they were moderate to high risk surgical candidates with a discrete lesion in the ICA. Both symptomatic subjects with ≥ 50% stenosis of the target lesion and asymptomatic subjects with ≥ 70% stenosis of the target lesion were eligible.

The protocol specified that follow-up visits occur at 1, 6 and 12 month post-procedure, and annually thereafter for up to three years or until device approval was obtained in the United States.

The primary endpoints were a composite of DSMI at 30 days and acute device success for the Accunet Embolic Protection System, defined as successful delivery, placement and retrieval of the device. Long-term outcome data, such as ipsilateral stroke and TLR at 6, 12, 24, and up to 36 months were collected in this study. The device success rate for the Acculink Stent (defined as attainment of a final result, < 50% residual stenosis covering the original lesion) was also assessed. The CEC adjudicated all 30-day post-procedure major endpoint events and any stroke during the follow-up period.

The results were descriptive in nature. The primary endpoint of a composite of DSMI at 30 days was 9.8%, including one death (fatal stroke) and two major ipsilateral strokes. There were two non-Q-wave MI. The device success rate for Accunet was 94.1%.

No subject had an ipsilateral stroke during the 31-day to 36-month follow-up period. Kaplan-Meier analysis predicted a freedom from ipsilateral stroke at 3 years of 94.1% for this subject cohort.

TLR rates were 0% and 4.3% at 6 and 12 months, respectively. There were no additional TLR events reported in the 12 month to 36 month follow-up period. Kaplan-Meier analysis estimated a freedom from TLR through 3 years of 95.7%.
The Accunet Embolic Protection System could be placed accurately and safely when used in conjunction with the Acculink Carotid Stent System for the treatment of ICA lesions in moderate to high-risk surgical subjects. The observed 30-day endpoint rate of 9.8% was acceptable. In addition, a 95.7% freedom from TLR and 94.1% freedom from ipsilateral stroke at 36 months support the potential long-term benefits of this procedure in preventing stroke in the moderate to high surgical risk population.

1.3.1.3 ARCHeR 1, 2 and 3 Pivotal Trials

The Acculink for Revascularization of Carotids in High Risk patients (ARCHeR) trials were conducted to evaluate whether using the Acculink Carotid Stent System with the Accunet Embolic Protection System was a safe and effective alternative in subjects at high risk for CEA. Both symptomatic subjects with ≥ 50% stenosis of the target lesion and asymptomatic subjects with ≥ 80% stenosis of the target lesion were eligible to enroll in the trial.

The ARCHeR Trials (IDE G980303) were a sequential series of three prospective, non-randomized, multicenter studies that consecutively enrolled 581 pivotal subjects between May 2000 to September 2003 at 43 sites in the United States sites and 5 sites in Canada.

The same Acculink Stent was used in all three trials. The initial series of 158 subjects (ARCHeR 1) underwent stenting with the OTW Acculink Carotid Stent System without adjunctive use of embolic protection. The OTW Accunet Embolic Protection System was introduced in the ARCHeR 2 Trial, in which 278 subjects were enrolled. Finally, the RX platform was introduced for both the stent and embolic protection systems in ARCHeR 3, in which 145 subjects were evaluated.

The objective for ARCHeR 1 and 2 was to establish that CAS was not inferior to CEA at 365 days. A weighted historical control (WHC) was used as a comparator; it was derived and calculated from a systematic review and analysis of the literature on CEA and medical therapy.

The objective of ARCHeR 3 was to establish that the RX platforms of the Acculink Carotid Stent System and Accunet Embolic Protection System were not inferior to the OTW platforms of these devices with respect to safety and efficacy at 30 days. The rate of DSMI at 30 days for ARCHeR 3 was compared to the results of ARCHeR 2 at the same 30-day time point to establish non-inferiority.

Clinical follow-up was conducted at the following intervals: 24 hours, 30 days, 6 months, 12 months and every 6 months thereafter for the duration of the follow-up period (a median of 726 days for ARCHeR 1, 378 days for ARCHeR 2 and 40 days for ARCHeR 3). The primary endpoint was DSMI at 30 days plus ipsilateral stroke between 31 and 365 days for ARCHeR 1 and 2. For ARCHeR 3, the primary endpoint was DSMI at 30 days. Secondary endpoints for all three trials included acute device and clinical success,
TLR at 6 and 12 months, ultrasound evaluation of the lesion at 6, 12 and 24 months (24 months for ARCHeR 1 and 2 only), and access site complications requiring treatment. Ipsilateral stroke occurring between 31 and 365 days was a specific secondary endpoint for the ARCHeR 3 trial. **Table 1.3-1** summarizes the trial designs of the ARCHeR 1, 2 and 3 trials.

Across the ARCHeR 1, 2 and 3 trials, 7.59%, 8.63%, and 8.28% of subjects, respectively, experienced a primary endpoint event (DSMI) within 30 days as are listed in **Table 1.3-2**. The primary composite endpoint rates for 30-day DSMI plus ipsilateral stroke at 1 year were 8.28% and 10.22%, respectively, for the ARCHeR 1 and 2 trials. The DSMI rate at 30 days for ARCHeR 3 was confirmed to be non-inferior to that of ARCHeR 2. The combined primary endpoint rate in all three studies was 9.6% (95% CI, 7.2%-12.0%) in comparison to a weighted historical control comparator. The 30-day rate of DSMI was 8.3% (95% CI, 6.2%-10.8%), and that of major stroke and death was 6.9% (95% CI, 5.0%-9.3%).

TLR at 12 months was 2.2% and 2.8%, respectively, for the ARCHeR 1 and 2 trials. Other secondary endpoints rates for ARCHeR 1, 2 and 3 are summarized in **Table 1.3-3**.
## Table 1.3-1. An Overview of the ARChER Trial Design

<table>
<thead>
<tr>
<th></th>
<th>ARChER 1</th>
<th>ARChER 2</th>
<th>ARChER 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Objective</strong></td>
<td>Non-inferiority to historical control</td>
<td>Non-inferiority to historical control</td>
<td>Non-inferiority to ARChER 2 results at 30 days</td>
</tr>
<tr>
<td><strong>Products Evaluated</strong></td>
<td>OTW Acculink Carotid Stent System</td>
<td>OTW Acculink and OTW Accunet Systems</td>
<td>RX Acculink and RX Accunet Systems</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Non-randomized, multicenter, single-arm, prospective clinical trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>158</td>
<td>278</td>
<td>145</td>
</tr>
<tr>
<td><strong>Number of Sites</strong></td>
<td>25 Sites in the U.S.</td>
<td>37 Sites in the U.S. and 1 Site in South America</td>
<td>19 Sites in the U.S., 4 Sites in Europe, and 1 Site in South America</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>30-day DSMI and 31-365 day ipsilateral stroke</td>
<td>30-day DSMI and 31-365 day ipsilateral stroke</td>
<td>30-day DSMI</td>
</tr>
<tr>
<td><strong>Secondary Endpoints-All Trials</strong></td>
<td>-Device Success</td>
<td>-Target Lesion Revascularization at 6 and 12 months</td>
<td>-Access Site complications requiring treatment</td>
</tr>
<tr>
<td></td>
<td>-Clinical Success</td>
<td>-6, 12 and 24 Month Ultrasound (annually thereafter)</td>
<td></td>
</tr>
<tr>
<td><strong>Specific Secondary Endpoints</strong></td>
<td>None</td>
<td>Medical Care Resource Utilization</td>
<td>31-365 day ipsilateral stroke</td>
</tr>
</tbody>
</table>
| **Subject Follow-up**    | -Neurologic evaluation by an independent neurologist and subject assessment at 24 hours, 30 days, 6 months, 12 months and every 6 months thereafter | -TIA/Stroke Questionnaire and adverse event assessment at 1, 3, 6, 9 and 12 months. | -ECG at 30 days  
- Ultrasound at 1, 6 and 12 months and annually thereafter |
### Table 1.3-2. ARCHeR Study Results - Primary Endpoint Event Rates

<table>
<thead>
<tr>
<th></th>
<th>ARCHeR 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 158)</td>
</tr>
<tr>
<td>30-day DSMI</td>
<td>7.59% (12/158)</td>
</tr>
<tr>
<td>[95% Conf. Interval]</td>
<td>[4.0%, 12.9%]</td>
</tr>
<tr>
<td>One-Year Primary Endpoint (30-day DSMI + 31-365 day Ipsilateral Stroke)</td>
<td>8.28% [-, 12.25%]</td>
</tr>
<tr>
<td>[Upper 95% CI]</td>
<td>10.22% [-, 13.48%]</td>
</tr>
<tr>
<td>Accunet Device Success</td>
<td>95.3% (264/277)</td>
</tr>
<tr>
<td>[95% Conf. Interval]</td>
<td>[92.1%, 97.5%]</td>
</tr>
</tbody>
</table>

### Table 1.3-3. ARCHeR Study Results – Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>ARCHeR 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 158)</td>
</tr>
<tr>
<td>Accunet Device Success</td>
<td>95.9% (139/145)</td>
</tr>
<tr>
<td>[95% Conf. Interval]</td>
<td>[91.2%, 98.5%]</td>
</tr>
<tr>
<td>30-day DSMI + 31-365 day Ipsilateral Stroke [Upper 95% CI]</td>
<td>9.88% [-, 14.49%]</td>
</tr>
<tr>
<td>Access Site Complication Requiring Treatment [95% Conf. Interval]</td>
<td>3.8% (6/158)</td>
</tr>
<tr>
<td></td>
<td>[1.4%, 8.1%]</td>
</tr>
<tr>
<td>Acceulink Device/Procedural Success</td>
<td>98.1% (153/156)</td>
</tr>
<tr>
<td>[95% Conf. Interval]</td>
<td>[94.5%, 99.6%]</td>
</tr>
<tr>
<td>Clinical Success</td>
<td>91.7% (143/156)</td>
</tr>
<tr>
<td>[95% Conf. Interval]</td>
<td>[86.2%, 95.5%]</td>
</tr>
<tr>
<td>Target Lesion Revascularization</td>
<td>0.7%</td>
</tr>
<tr>
<td>at 6 months</td>
<td>2.2%</td>
</tr>
<tr>
<td>at 12 months</td>
<td>3.0%</td>
</tr>
<tr>
<td>Ultrasound (Same or decreased stenosis from 1 month exam)</td>
<td>82.4% (84/102)</td>
</tr>
<tr>
<td>at 6 months</td>
<td>73.0% (143/196)</td>
</tr>
<tr>
<td>at 12 months</td>
<td>80.4% (78/97)</td>
</tr>
</tbody>
</table>

*Data contained in ARCHeR Long-Term Follow-Up Study in Section 1.3.2.*
Results from the ARChE R 1, 2, and 3 Trials demonstrated that the Acculink and RX Acculink Carotid Stent Systems when used with the Accunet and RX Accunet Embolic Protection Systems are safe and effective in treating carotid artery disease for subjects at high risk for CEA. Furthermore, CAS with embolic protection is not inferior to historical results of CEA in a similar patient population, suggesting that carotid artery stenting is a safe, durable, and effective alternative in high surgical risk subjects.

1.3.2  Acculink/Accunet Post-Approval Clinical Studies Overview

Four Abbott Vascular studies have been conducted since the approval of the RX Acculink and the clearance of the RX Accunet for treatment of carotid stenosis in a high risk subject population. These studies have enrolled a total of 16,723 subjects under commercial use circumstances between 2004 and 2010. Three of the studies, ARChE R Long-Term Follow-Up, CAPTURE, and CAPTURE 2 have completed enrollment and are closed. The CHOICE Study remains open to enrollment.

1.3.2.1  ARChE R Long-Term Follow-Up Study

As a condition of PMA approval, Abbott Vascular executed a study, the ARChE R Long-Term Follow-Up (LTFU) Study (IDE G980303) to provide longer term data (36 months) for subjects implanted with the Acculink Stent in the ARChE R 1, 2, and 3 Trials. The purpose of the ARChE R LTFU study was to evaluate the long-term safety and efficacy of carotid artery stenting in high risk subjects previously enrolled to an ARChE R study, and currently implanted with an Acculink Stent.

Of the 581 subjects enrolled in the ARChE R trials, 230 subjects without a completed 3 year follow-up were enrolled in the LTFU study. The primary endpoint was the annual rate of fatal and non-fatal ipsilateral stroke. The secondary endpoint was clinically driven TLR. The rate of clinically driven TLR continued to be low, at a cumulative rate of 2.8% at two years and 3.0% at three years, respectively. Kaplan-Meier analysis showed the annualized rates of non-peri-procedural ipsilateral stroke and non-peri-procedural major ipsilateral stroke through 36 month follow-up were 1.1% and 0.4%, respectively. Ultrasound data at 12, 24 and 36 months demonstrated that the stented lesion was relatively stable beyond 12 months.

The long-term follow-up data provided support for the long-term safety, effectiveness and long-term durability of CAS procedure. In addition, continued stroke prevention was maintained for the patient population that would otherwise be at high risk for surgical treatment with CEA.

1.3.2.2  CAPTURE Trial

The Carotid RX Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE, P040012/S1) was a post-approval trial, which was designed to:
• Confirm that the RX Acculink Carotid Stent System and the RX Accunet Embolic Protection System can be used safely by physicians with varying levels of experience;
• To identify rare or unanticipated device-related events that might occur with the use of the RX Acculink Carotid Stent System and the RX Accunet Embolic Protection System; and
• To evaluate the adequacy of the Abbott Vascular Physician Training Program.

The primary endpoint was DSMI within 30 days post-procedure. Enrollment began in October 2004 and concluded in December 2006. A total of 4331 subjects with \( \geq 50\% \) symptomatic or \( \geq 80\% \) asymptomatic carotid stenosis high risk for CEA were enrolled in this trial at 144 sites; subject follow-up was completed in April 2007. A CEC adjudicated all strokes, TIs, suspected strokes, and suspected TIsAs reported by the sites. Physicians participating in the study were categorized as Level 1, 2, or 3 based on their level of experience and training (Level 3 indicates the lowest level of experience and training).

The primary composite endpoint rate (DSMI) for the evaluable cohort of 4225 subjects in CAPTURE was 6.1% at 30 days. There was no evidence of a statistically significant difference among endpoint rates for Level 1, 2 and 3 physicians; there also was no evidence that physician experienced level was a predictor of outcomes in a multivariable logistic regression analysis. The following rare events were reported: hyperperfusion syndrome 0.06%, surgery (CEA) 0.03% and in-stent thrombosis 0.03%.

The results from CAPTURE confirmed that the RX Acculink when used with the RX Accunet devices can be used safely by a broad group of physicians under commercial use conditions. The CAPTURE Trial has completed follow-up and is now closed.

1.3.2.3 CAPTURE 2 Trial

CAPTURE 2 (P040012/S2) was also a post-approval trial designed to gather additional data for high surgical risk subjects having carotid artery stenting. The CAPTURE 2 Trial has completed follow-up and is now closed. Subjects were followed for 30 days after the index procedure. The primary endpoint for the CAPTURE 2 study was a composite DSMI at 30 days post-procedure. A CEC adjudicated all strokes and suspected strokes reported by study sites. Since March 9, 2006, a total of 6361 subjects, who were either symptomatic with \( \geq 50\% \) carotid stenosis or asymptomatic with \( \geq 80\% \) carotid stenosis and were at high risk for CEA were enrolled and treated at 286 United States sites by 476 physicians, as reported in the final report for CAPTURE 2 submitted in the 2010 PMA Annual Report (P040012).

The primary endpoint DSMI at 30 days was 3.6%, the rate of all death and stroke was 3.4% and the combined rate of death and major stroke was 1.4%. A non-hierarchical tally was 0.8% death, a stroke rate of 2.8% (0.8% defined as major and 2.0% as minor), and a MI rate of 0.4%.

Octogenarians showed a higher DSMI rate than non-octogenarians (4.7% vs. 3.2%) as
well as higher rate for death and all stroke (4.6% vs. 3.0%) and rate for death and major stroke (1.9% vs. 1.3%). The same is true for the differences in all stroke (3.9% vs. 2.5%), major stroke (1.2% vs. 0.7%), and minor stroke (2.7% vs. 1.8%). The differences in the DSMI, death and stroke and all stroke rates are statistically significant.

The CAPTURE 2 study evaluated outcomes of CAS in a large cohort of subjects representing “real world” experience with RX Acculink when used with the Accunet devices. These results further demonstrate that carotid stenting with the RX Acculink when used with the Accunet Systems can be performed safely and effectively by a variety of specialists in a community hospital setting with results that match or exceed results from investigational carotid stent studies in a high risk population.

1.3.2.4 CHOICE

The CHOICE Study is an ongoing post-market study using commercially available Abbott Vascular carotid stent and embolic protection systems. CHOICE is a prospective, non-randomized, multicenter, descriptive, post-approval study of two carotid artery stent systems.

The purpose of the CHOICE study is to collect additional data on Abbott Vascular carotid stent systems when used by a broad group of physicians under commercial use conditions.

The Abbott Vascular devices being used in the CHOICE Study are:
- RX Acculink Carotid Stent System
- RX Accunet Embolic Protection System
- Xact Carotid Stent System
- Emboshield Embolic Protection Systems

The study endpoint is a composite of DSMI at 30 days.

Subjects undergo a neurological assessment pre-procedure, at 24 hours and 30 days post-procedure. During the 30-day follow-up, any occurrence of death, stroke, MI, new neurologic event, and device-related adverse event is collected. All strokes and suspected strokes are adjudicated by a CEC.

The first subject was enrolled in October 2006 and enrollment is ongoing. No end date has been determined for the CHOICE Study and enrollment is open-ended at approved sites. As of January 10, 2010, the number of subjects enrolled was 6872 at 233 sites by 560 physicians in the United States.

The evaluable cohort consists of subjects who either completed 30-day follow-up, or experienced an endpoint event within 30 days post-procedure. A total of 97% (6639/6872) of subjects are evaluable. The DSMI rate is 3.7% at 30 days. Non-hierarchically, the death rate is 0.9%, the stroke rate is 2.7% (major stroke 0.9% and
minor stroke 1.9%). The MI rate is 0.6%. Octogenarians showed a higher DSMI rate than non-octogenarians (6.3% vs. 2.9%) as well as higher rate for death and all stroke, and death and major stroke. The same is true for the differences in all stroke (5.1% vs. 2.0%), major stroke (1.8% vs. 0.6%), and minor strokes (3.4% vs. 1.4%). The results continue to demonstrate the safety of carotid artery stenting when used by physicians with a broad range of experience in a commercial use setting.

1.3.3  History of CREST

CREST was conceived in the same timeframe as ARCHeR to study the use of carotid stents for treating disease in extracranial internal carotid arteries due to atherosclerosis in the standard surgical risk population. CREST was designed in 1999 to address a segment of the population, characterized by subjects with a clinically significant degree of carotid stenosis, but without the multiple co-morbidities placing the high risk population in jeopardy of adverse events from CEA. The same devices, the Acculink and RX Acculink Carotid Stent Systems and the Accunet and RX Accunet Embolic Protection Systems have been studied exclusively in CREST to demonstrate the safety and effectiveness of carotid stenting in this new patient population of standard risk subjects.

CREST was initially designed by Robert Hobson II, MD (deceased) in collaboration with the U.S. National Institute of Neurological Disorders of the National Institute of Health as an academic, landmark study to contrast the clinical result of interventional treatment with stents to the standard of care at that time, carotid endarterectomy, over a multi-year period. The study was initially funded through an investigator-originated grant, and later by the NIH and Abbott Vascular.

The design of CREST was a prospective, randomized (1 CAS: 1 CEA), parallel, two-arm, multi-center trial, with blinded endpoint evaluation. A Lead-In Phase was designed to allow for clinical center start-up and physician credentialing as many interventionalists participating in the trial were inexperienced in carotid stenting, an emerging therapy at that time.

The organizational structure of CREST is complex involving several entities including Abbott Vascular as the initial study sponsor, governmental agencies (FDA, NIH and CMS), academic scientists, clinical investigators and a multitude of peer review committees. These committees provide oversight to assure the scientific integrity of the trial and to monitor the safety and effectiveness of the treatments under evaluation. Additional information about the specific function and responsibilities of the Steering Committees is summarized in Section 3.2.2 of this report.

Following approval of IDE G000080, in December 2000 CREST initiated enrollment of standard risk subjects in tandem with enrollment of high risk subjects in the first feasibility (ARCHeR) studies involving the Acculink and Accunet Systems. CREST was initially approved to enroll up to 20 lead-in subjects per enrolling interventionalist and up to 2500 subjects in the randomized phase.
In April 2003, the FDA approved the transfer of the CREST IDE to Dr. Hobson of the University of Medicine and Dentistry of New Jersey (UMDNJ). Transfer of CREST to Dr. Hobson streamlined the study organizational structure and ultimately expedited completion of enrollment in the trial in July 2008. Abbott Vascular retained its responsibility to manufacture and supply the investigational devices through the duration of the trial.

The CREST Protocol and its subsequent amendments are summarized in Sections 2.0 and 3.0 of this report. The Abbott Vascular methodology for the analysis of CREST is presented in Section 2.3; the results of the primary analysis can be found in Section 5.0 of this report.