Prior Authorization Review
Panel MCO Policy Submission

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Type of Submission – Check all that apply:
- [ ] New Policy
- [X] Revised Policy*
- [ ] Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 491 Coronary Artery Brachytherapy and Other Adjuncts to Coronary Interventions**

This CPB has been revised to state that the following are considered experimental and investigational: (i) the use of abciximab for thrombus resolution during intracranial bypass surgery; and (ii) abciximab/heparin therapy for left ventricular assist device implantation in individuals with heparin-induced thrombocytopenia.

Name of Authorized Individual (Please type or print): Dr. Bernard Lewin, M.D.

Signature of Authorized Individual: [Signature]

www.aetnabetterhealth.com/pennsylvania  Revised 05/10/18
Aetna considers coronary artery brachytherapy (i.e., intra-coronary radiation) in native coronary arteries or coronary artery bypass grafts medically necessary as adjunctive treatment during a second angioplasty/stent placement when blockage has re-occurred within the localized area of a previously placed bare metal stent (i.e., in-stent re-stenosis).
Aetna considers coronary artery brachytherapy experimental and investigational for use with drug-eluting stents, and for the primary prevention of re-stenosis and all other indications (except for those listed in policy section above) due to insufficient evidence in the peer-reviewed literature.

Aetna considers abciximab (ReoPro) medically necessary as an adjunctive treatment for persons undergoing percutaneous angioplasty/stent placement.

Aetna considers the use of abciximab experimental and investigational for the following indications (not an all-inclusive list) because there is currently insufficient evidence from randomized controlled trials regarding its safety or effectiveness for these indications.

- Acute ischemic stroke
- Acute limb ischemia
- Acute myocardial infarction without percutaneous intervention
- Cardiac complications (e.g., coronary artery aneurysms) of Kawasaki disease
- Saphenous vein graft interventions
- Stenting of superficial femoral occlusive disease
- Thromboembolic complications during cerebral aneurysm coiling
- Thrombus resolution during intracranial bypass surgery

Aetna considers abciximab/heparin therapy for left ventricular assist device implantation in individuals with heparin-induced
thrombocytopenia experimental and investigational because the effectiveness of this approach has not been established.

Background

Intracoronary brachytherapy is used to prevent restenosis of an artery after angioplasty or stent placement by delivering a small amount of radiation to the treated area, which may reduce the need for additional angioplasty or bypass surgery. The radiation is intended to discourage the overgrowth of normal tissue as the healing process occurs.

When treating coronary artery disease with angioplasty or stents, the recurrence of coronary artery blockage at the site of treatment remains a significant risk. Recurrent coronary stenosis occurs in 20 to 30 % of patients in whom stents have been implanted for the treatment of obstructive lesions; when it occurs within the stent, it is referred to as in-stent re-stenosis. According to generally accepted guidelines, if re-stenosis occurs within a stent, it can usually be treated by pharmacotherapy and/or repeat angioplasty followed by brachytherapy.

A special catheter is used to radiate a localized area. The catheter is passed into the coronary arteries and across the target area. Once the targeted area of stenosis is “bracketed” by the catheter, the radiation is applied.

Two types of radiation that have been used for in-stent re-stenosis: (i) gamma radiation and (ii) beta radiation. Of the 2 Food and Drug Administration (FDA)-approved devices, the
Checkmate System (Cordis Corporation) uses gamma radiation and the Beta-Cath System (Novoste Corporation) uses beta radiation. Approval by the FDA for both of these devices is limited to use in stents that have been implanted in the past, and that have now re-stenosed. The radiation is believed to inhibit the cellular proliferation that causes re-blockage of the vessel.

In its FDA submission for the Checkmate System, the Cordis Corporation cited 6-month angiographic results of 3 landmark single- and multi-center randomized clinical trials (GAMMA-I with 252 patients, WRIST with 130 patients, and SCRIPPS-I with 60 patients). Results from these trials consistently showed a significant reduction in both angiographic and clinical in-stent re-stenosis versus placebo, as well as reduced major adverse clinical events. In the GAMMA-I trial, the rate of re-stenosis was reduced by 42% by coronary artery radiation. In the patients treated with gamma radiation, 24% experienced re-stenosis, whereas in the control group not treated with radiation, 42% had re-stenosis. The device is indicated for the delivery of therapeutic doses of gamma radiation for the purpose of reducing in-stent re-stenosis. The system is for use in the treatment of native coronary arteries (2.75 to 4.0 mm in diameter and lesions up to and including 45 mm in length) with in-stent re-stenosis following percutaneous re-vascularization using current interventional techniques.
The FDA approved product labeling for the Cordis Checkmate System states that the device should not be used in patients who are not good candidates for blood-thinning drugs or anti-platelet therapy.

In its FDA submission for the Novoste Beta-Cath System, the Novoste Corporation cited data from the START trial, a multi-center, randomized, placebo-controlled trial involving 476 patients. At 8 months, re-stenosis had occurred in 14 % of the stented segments in patients who had received radiation, as compared with 41 % of the controls. The device is indicated to deliver beta radiation to the site of successful percutaneous coronary intervention for the treatment of in-stent re-stenosis in native coronary arteries with discrete lesions (treatable with a 20 mm balloon) in a reference vessel diameter ranging from 2.7 mm to 4.0 mm.

The FDA-approved product labeling for the Beta-Cath System states that it should not be used for patients with unprotected left main coronary artery disease (50 % narrowing of the coronary artery) or for patients who are not candidates for blood-thinning drugs or anti-platelet therapy.

A randomized, multi-center, placebo-controlled trial of 1,455 patients reported the use of intra-coronary beta-radiation for the “primary prevention” of re-stenosis. Results compared the outcomes of: (i) total radiation cohort (those receiving either angioplasty or a stent); (ii) those receiving angioplasty and radiation; and (iii) those receiving angioplasty, stent and radiation. The clinical results did not reach statistical significance in the total cohort (target lesion re-
vascularization rate 13.7 % versus 15.4 % placebo control).

In those patients receiving angioplasty and radiation, the rate of in-lesion re-stenosis was significantly reduced (21.4 % versus 34.3 % placebo control). In the group receiving angioplasty, stent and radiation, the radiation had a positive effect on preventing re-stenosis at the initial lesion site (21.1 % versus 33.0 % placebo control), but had a negative effect on the adjacent edges, leading to higher clinical re-stenosis compared with placebo (44.9 % versus 35.3 %).

Coronary artery brachytherapy has been shown to be effective in preventing re-stenosis in coronary artery bypass grafts. Waksman et al (2002) reported on the results of the SVC-WRIST Trial, a randomized controlled clinical trial of the effects of intra-coronary gamma brachytherapy in 120 patients with in-stent re-stenosis of saphenous vein grafts. After 6 months, the re-stenosis rate was lower in the 60 patients assigned to gamma brachytherapy than in the 60 assigned to placebo (21 % versus 44 %, p = 0.005). At 12 months, the rate of revascularization of the target lesion was 70 % lower in the gamma brachytherapy group than in the placebo group (17 % versus 57 %, p < 0.001), and the rate of major cardiac events was 49 % lower (32 % versus 63 %, p < 0.001). The investigators concluded that these results support the use of brachytherapy for the treatment of in-stent re-stenosis in patients with bypass grafts.
Castagna et al (2002) reported on the 6-month follow-up of 45 of 120 patients in the SVC-WRIST trial with restenotic lesions of saphenous vein grafts who were evaluated by intra-vascular ultrasound (IVUS). (Because the SVC-WRIST Trial protocol did not mandate IVUS, not all trial participants were evaluated with this procedure). The investigators reported a significant reduction in repeat stenosis in the patients randomized to gamma brachytherapy compared to placebo; they reported that the effectiveness of gamma brachytherapy in patients with re-stenosis of saphenous vein grafts was similar to that reported in other trials of gamma radiation therapy in patients with re-stenosis of native coronary lesions. The investigators concluded that intra-vascular brachytherapy effectively reduced intimal hyperplasia re-accumulation in vein graft in-stent re-stenosis with no deleterious effect on reference segments within 6 months.

Oliver and colleagues (2008) performed a meta-analysis of randomized trials assessing the outcome of vascular brachytherapy (VBT) or drug-eluting stents (DES) for the treatment of coronary artery in-stent restenosis (ISR). Studies utilising DES or VBT for ISR were identified by a systematic search. Data was pooled and combined overall effect measures were calculated for a random effect model in terms of deaths, myocardial infarctions, re-vascularization, binary restenosis, mean late luminal loss and major adverse cardiac events (MACE). A total of 14 eligible studies (3,103 patients) were included. Neither therapy had any effect on mortality or myocardial infarction rate. Vascular brachytherapy reduced the rate of re-vascularisation (RR 0.59, 95 % confidence
interval [CI]: 0.50 to 0.68), MACE (RR 0.58, 95 % CI: 0.51 to 0.67), binary re-stenosis (RR 0.51, 95 % CI: 0.44 to 0.59) and late loss (-0.73 mm, 95 % CI: -0.91 to -0.55 mm) compared to balloon angioplasty and selective bare metal stents (BMS) alone at intermediate follow-up and MACE (RR 0.72, 95 % CI: 0.61 to 0.85) at long-term follow-up. Drug-eluting stents reduced the rate of re-vascularisation (odds ratio [OR] 0.51, 95 % CI: 0.36 to 0.71), MACE (OR 0.55, 95 % CI: 0.39 to 0.79) and binary re-stenosis (OR 0.57, 95 % CI: 0.40 to 0.81) compared to VBT but follow-up was limited to 9 months. The authors concluded that VBT improves the long-term outcome of angioplasty compared with BMS alone in the treatment of ISR. Drug-eluting stents appear to provide similar results to that of VBT during short-term follow-up.

Beta-radiation is considered investigational in the prevention of de novo lesions in patients at a higher risk of re-stenosis undergoing angioplasty and/or stenting. While the initial data are promising in those patients receiving angioplasty and radiation, further randomized, multi-center, placebo-controlled trials to investigate the long-term effects of radiation and the risk of edge re-stenosis in the treatment of primary prevention of re-stenosis are needed.

Many questions concerning the safety (e.g., late thrombosis, re-stenosis at the proximal and distal edges of irradiated zones, myocardial infarction) of radiation for in-stented re-stenosis have been raised in the literature. Some authorities believe that, until these questions can be answered by additional randomized well-controlled clinical trials with larger numbers of
patients, in different populations, and with long-term follow-up, physicians should remain cautious in their use of this technique.

**Anti-platelet Therapy**

Intravenous platelet glycoprotein IIb/IIIa receptor inhibitors have been demonstrated to reduce the incidence of ischemic complications when used in conjunction with coronary interventions. ReoPro (abciximab) is a monoclonal antibody that forms a complex with glycoprotein IIb/IIIa receptors at the surface of blood platelets. Because ReoPro blocks these receptors it prevents the platelets from adhering to each other and from forming blood clots. According to the FDA-approved product labeling, ReoPro is indicated as an adjunct to percutaneous coronary interventions for the prevention of cardiac ischemic complications:

- In patients undergoing percutaneous coronary intervention.
- In patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours.

Use of abciximab in patients not undergoing percutaneous coronary intervention has not been studied. Abciximab is intended for use with aspirin and heparin and has been studied only in that setting.

Stent implantation in the superficial femoral artery has been associated with suboptimal results while glycoprotein IIb/IIIa inhibitors have shown improved procedural results during
coronary intervention. In a randomized, placebo-controlled trial, Ansel et al (2006) assessed the effect of abciximab during nitinol stenting of superficial femoral occlusive disease. Major outcome measures included 9-month re-stenosis defined as a decrease in ankle brachial index and in-stent duplex ultrasound restenosis, and adverse events defined as death (30 days) or repeat re-vascularization within 9 months. A total of 27 patients were randomized to abciximab and 24 patients to control (placebo). The primary end point of cumulative re-stenosis occurred in 15.4 % of patients given abciximab and in 12 % administered placebo (p = 0.873). The primary re-stenosis endpoint in diabetics and total occlusions were similar at 14.3 % and 15.4 %, respectively. The composite end point of 30-day mortality and 9-month re-vascularization occurred in 5.8 % abciximab and 0 % (p = 0.274) placebo with no 30-day deaths. Graded treadmill time and Rutherford class were all significantly improved in both groups, but the abciximab group did not appear to demonstrate any identifiable effect. The authors concluded that nitinol stenting of the superficial femoral artery was associated with favorable functional outcomes at 9 months. Adjunctive abciximab did not appear to demonstrate any identifiable effect.

In a Cochrane review on glycoprotein IIb/IIIa inhibitors for acute ischemic stroke (Ciccone et al, 2006), the authors concluded that there is currently insufficient evidence from randomized controlled trials regarding the safety or efficacy of glycoprotein IIb/IIIa inhibitors therapy in the management of patients with acute ischemic stroke.
Seitz and Siebler (2008) reviewed the literature concerning the use of intravenously administered GPIIb/IIIa-receptor antagonists abciximab, eptifibatide and tirofiban for the treatment of patients with acute ischemic brain infarction. In multi-center, prospective, randomized and placebo-controlled trials, abciximab had a higher cerebral bleeding risk, while tirofiban did not increase hemorrhage. When combined with fibrinolysis, abciximab and tirofiban were found to improve cerebral artery re-canalization and tissue re-perfusion resulting in reduced infarct volumes and improved neurological outcome. Thus, GPIIb/IIIa-receptor antagonists have a great potential for the treatment of acute stroke.

In a phase-III clinical trial, Adams and colleagues (2008) examined the relative safety and effectiveness of abciximab in patients with acute ischemic stroke with planned treatment within 5 hours since symptoms onset. The planned enrollment was 1,800 patients. The primary cohort enrolled those patients who could be treated within 5 hours of stroke onset. A companion cohort enrolled participants who were treated 5 to 6 hours after stroke as well as a smaller cohort of patients who could be treated within 3 hours of stroke present on awakening. The primary outcome measure was the dichotomous modified Rankin Scale score at 3 months as adjusted to the baseline severity of stroke among subjects in the primary cohort. The primary safety outcome was the rate of symptomatic or fatal intra-cranial hemorrhage that occurred within 5 days of stroke. The trial was terminated prematurely after 808 patients in all cohorts were enrolled by recommendation.
of an independent safety and effectiveness monitoring board due to an unfavorable benefit-risk profile. At 3 months, approximately 33% of patients assigned placebo (72/218) and 32% of patients assigned abciximab (71/221; p = 0.944) in the primary cohort were judged to have a favorable response to treatment. The distributions of outcomes on the modified Rankin Scale were similar between the treated and control groups. Within 5 days of enrollment, approximately 5.5% of abciximab-treated and 0.5% of placebo-treated patients in the primary cohort had symptomatic or fatal intra-cranial hemorrhage (p = 0.002). The trial also did not demonstrate an improvement in outcomes with abciximab among patients in the companion and wake-up cohorts. Although the number of patients was small, an increased rate of hemorrhage was noted within 5 days among patients in the wake-up population who received abciximab (13.6% versus 5% for placebo). The authors concluded that this trial did not demonstrate either safety or effectiveness of intravenous administration of abciximab for the treatment of patients with acute ischemic stroke regardless of end point or population studied. There was an increased rate of symptomatic or fatal intra-cranial hemorrhage in the primary and wake-up cohorts.

Schulz et al (2010) noted that the in the Bavarian Reperfusion Alternatives Evaluation (BRAVE)-3 study, up-stream administration of abciximab additional to 600 mg clopidogrel loading did not reduce the infarct size in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary interventions (PCI). The aim of this study was to
investigate 1-year clinical outcomes in the BRAVE-3 study patients. A total of 800 patients with acute STEMI within 24 hrs from symptom onset, all treated with 600 mg of clopidogrel were randomized in a double-blind fashion to receive either abciximab (n = 401) or placebo (n = 399) in the intensive care unit before being sent to the catheterization laboratory. The main outcome of interest of the present study, the composite of death, recurrent myocardial infarction, stroke or re-vascularization of the infarct-related artery (IRA) at 1 year, was 23.0 % (92 patients) in the abciximab versus 25.7 % (102 patients) in the placebo group [relative risk (RR) = 0.90, 95 % CI: 0.67 to 1.20; p = 0.46]. The combined incidence of death, recurrent myocardial infarction or stroke was 9.3 % in the abciximab group versus 6.0 % in the placebo group (RR = 1.55, 95 % CI: 0.93 to 2.58; p = 0.09). There was a significant reduction of the IRA re-vascularization with abciximab compared to placebo (16.3 versus 22.3 %, RR = 0.71, 95 % CI: 0.52 to 0.98; p = 0.04). The authors concluded that in patients with STEMI, all receiving 600 mg clopidogrel, abciximab did not improve overall clinical outcomes at 1 year after PCI.

Dong et al (2010) performed a meta-analysis to evaluate the relative safety and efficacy of up-stream versus deferred administration of small-molecule glycoprotein IIb/IIIa inhibitors (smGPIs) in STEMI patients. A total of 10 randomized clinical trials comparing up-stream versus deferred administration of smGPIs in 2,724 patients were located in the electronic databases of the published literature. Pre-procedural Thrombolysis In Myocardial Infarction Study (TIMI) grade 2 or 3 flow was present in 45.0 % of
the up-stream group compared with 36.9 % in the deferred group (OR 1.40, p < 0.001). However, no difference in post-procedural TIMI 3 flow (OR 0.87, p = 0.25) was found between the groups. The 30-day mortality rate in the up-stream group did not differ from that of the deferred group (OR 1.04, p = 0.85). No significant difference was noted with respect to major bleeding complications (OR 1.25, p = 0.38). The authors concluded that in STEMI patients scheduled for primary PCI, although early smGPIs treatment improved initial epicardial patency, no beneficial effect on post-procedural angiographic or 30-day clinical outcome was found. Thus, the current available data do not support the routine utilization of up-stream smGPIs in STEMI patients treated with primary PCI.

Thiele and colleagues (2012) examined the safety and effectiveness of intra-coronary (IC) versus standard intravenous (IV) bolus application in patients with ST-elevation myocardial infarction (STEMI) undergoing this intervention. The AIDA STEMI trial was a randomized, open-label, multi-center trial. Patients presenting with STEMI in the previous 12 hrs with no contraindications for abciximab were randomly assigned in a 1:1 ratio by a central web-based randomization system to IC versus IV abciximab bolus (0.25 mg/kg bodyweight) during PCI with a subsequent 12 hrs IV infusion 0.125 μg/kg/min (maximum 10 μg/min). The primary endpoint was a composite of all-cause mortality, recurrent infarction, or new congestive heart failure within 90 days of randomization. Secondary endpoints were the time to occurrence of the primary endpoint, each individual component of that endpoint,
early ST-segment resolution, TIMI flow grade, and enzymatic infarct size. A masked central committee adjudicated the primary outcome and its components. Treatment allocation was not concealed from patients and investigators. Between July, 2008 and April, 2011, a total of 2,065 patients were randomly assigned IC abciximab (n = 1032) or IV abciximab (n = 1033). Intra-coronary, as compared with IV abciximab, resulted in a similar rate of the primary composite clinical endpoint at 90 days in 1,876 analysable patients (7.0 % versus 7.6 %; OR 0.91; 95 % CI: 0.64 to 1.28; p = 0.58). The incidence of death (4.5 % versus 3.6 %; 1.24; 0.78 to 1.97; p = 0.36) and re-infarction (1.8 % versus 1.8 %; 1.0; 0.51 to 1.96; p = 0.99) did not differ between the treatment groups, whereas less patients in the IC group had new congestive heart failure (2.4 % versus 4.1 %; 0.57; 0.33 to 0.97; p = 0.04). None of the secondary endpoints or safety measures differed significantly between groups. The authors concluded that in patients with STEMI undergoing primary PCI, IC as compared to IV abciximab did not result in a difference in the combined endpoint of death, re-infarction, or congestive heart failure. Since IC abciximab bolus administration is safe and might be related to reduced rates of congestive heart failure the IC route might be preferred if abciximab is indicated in high-risk patients.

Stone and colleagues (2012) examined if bolus IC abciximab, manual aspiration thrombectomy, or both reduce infarct size in high-risk patients with STEMI. Between November 28, 2009, and December 2, 2011, a total of 452 patients presenting at 37 sites in 6 countries within 4 hrs of STEMI due to proximal or mid left anterior
descending artery occlusion undergoing primary PCI with bivalirudin anti-coagulation were randomized in an open-label, 2:2 factorial design to bolus IC abciximab delivered locally at the infarct lesion site versus no abciximab and to manual aspiration thrombectomy versus no thrombectomy. A 0.25-mg/kg bolus of abciximab was administered at the site of the infarct lesion via a local drug delivery catheter. Manual aspiration thrombectomy was performed with a 6-F aspiration catheter. Primary end point were infarct size (percentage of total left ventricular mass) at 30 days assessed by cardiac magnetic resonance imaging (cMRI) in the abciximab versus no abciximab groups (pooled across the aspiration randomization); major secondary end point were 30-day infarct size in the aspiration versus no aspiration groups (pooled across the abciximab randomization). Evaluable cMRI results at 30 days were present in 181 and 172 patients randomized to IC abciximab versus no abciximab, respectively, and in 174 and 179 patients randomized to manual aspiration versus no aspiration, respectively. Patients randomized to IC abciximab compared with no abciximab had a significant reduction in 30-day infarct size (median, 15.1%; interquartile range (IQR), 6.8% to 22.7%; n = 181, versus 17.9% (IQR, 10.3% to 25.4%); n = 172; p = 0.03). Patients randomized to IC abciximab also had a significant reduction in absolute infarct mass (median, 18.7 g (IQR, 7.4 to 31.3 g); n = 184, versus 24.0 g (IQR, 12.1 to 34.2 g); n = 175; p = 0.03) but not abnormal wall motion score (median, 7.0 (IQR, 2.0 to 10.0); n = 188, versus 8.0 (IQR, 3.0 to 10.0); n = 184; p = 0.08). Patients randomized to aspiration thrombectomy versus no aspiration had no
significant difference in infarct size at 30 days (median, 17.0 % (IQR, 9.0 % to 22.8 %); n = 174, versus 17.3 % (IQR, 7.1 % to 25.5 %); n = 179; p = 0.51), absolute infarct mass (median, 20.3 g (IQR, 9.7 to 31.7 g); n = 178, versus 21.0 g (IQR, 9.1 to 34.1 g); n = 181; p = 0.36), or abnormal wall motion score (median, 7.5 (IQR, 2.0 to 10.0); n = 186, versus 7.5 (IQR, 2.0 to 10.0); n = 186; p = 0.89). The authors concluded that in patients with large anterior STEMI presenting early after symptom onset and undergoing primary PCI with bivalirudin anti-coagulation, infarct size at 30 days was significantly reduced by bolus IC abciximab delivered to the infarct lesion site but not by manual aspiration thrombectomy. Moreover, the authors stated that larger trials are needed to examine if the degree of infarct size reduction at 30 days achieved with intracoronary abciximab in the present study translate into improved late clinical outcomes without increasing bleeding.

De Luca et al (2012) performed a meta-analysis of randomized controlled trials (RCTs) to assess the safety and effectiveness of IC vs IV abciximab administration in STEMI patients undergoing primary angioplasty. These researchers obtained results from all RCTs enrolling STEMI patients undergoing primary PCI. The primary endpoint was mortality, while recurrent myocardial infarction, post-procedural epicardial (TIMI 3) and myocardial (MBG 2-3) perfusion were identified as secondary endpoints. The safety endpoint was the risk of major bleeding complications. A total of 8 RCTs were finally included in the meta-analysis, enrolling a total of 3,259 patients. As compared to IV route, IC abciximab was associated with a significant
improvement in myocardial perfusion (OR (95% CI) = 1.76 (1.28 to 2.42), p < 0.001), without significant benefits in terms of mortality (OR (95% CI) = 0.85 (0.59 to 1.23), p = 0.39), re-infarction (OR (95% CI) = 0.79 (0.46 to 1.33), p = 0.37), or major bleeding complications (OR (95% CI) = 1.19 (0.76 to 1.87), p = 0.44). However, these investigators observed a significant relationship between patient's risk profile and mortality benefits from IC abciximab administration (p = 0.011). The authors concluded that the present updated meta-analysis showed that IC administration of abciximab is associated with significant benefits in myocardial perfusion, but not in clinical outcome at short-term follow-up as compared to IV abciximab administration, without any excess of major bleedings in STEMI patients undergoing primary PCI. However, a significant relationship was observed between patient's risk profile and mortality benefits from IC abciximab administration. Therefore, waiting for long-term follow-up results and additional randomized trials, IC abciximab administration can not be routinely recommended, but may be considered in high-risk patients.

Eitel et al (2013) noted that the aim of the AIDA STEMI (Abciximab IV versus IC. in ST-elevation Myocardial Infarction) cardiac magnetic resonance (CMR) substudy was to investigate potential benefits of IC versus IV abciximab bolus administration on infarct size and reperfusion injury in ST-segment elevation myocardial infarction. The AIDA STEMI trial randomized 2,065 patients to IC or IV abciximab and found similar rates of major adverse cardiac events at 90 days with significantly less congestive heart failure in the IC. abciximab group. Cardiac
magnetic resonance can directly visualize myocardial damage and re-perfusion injury, thereby providing mechanistic and pathophysiological insights. These investigators enrolled 795 patients in the AIDA STEMI CMR substudy; CMR was completed within 1 week after ST-segment elevation myocardial infarction. Central core laboratory-masked analyses for quantified ventricular function, volumes, infarct size, microvascular obstruction, hemorrhage, and myocardial salvage were performed. The area at risk (p = 0.97) and final infarct size (16 % [interquartile range: 9 % to 25 %] versus 17 % [interquartile range: 8 % to 25 %], p = 0.52) did not differ significantly between the IC and the IV abciximab groups. Consequently, the myocardial salvage index was similar (52 [interquartile range: 35 to 69] versus 50 [interquartile range: 29 to 69], p = 0.25). There were also no differences in microvascular obstruction (p = 0.19), intra-myocardial hemorrhage (p = 0.19), or ejection fraction (p = 0.95) between both treatment groups. Patients in whom major adverse cardiac events occurred had significantly larger infarcts, less myocardial salvage, and more pronounced ventricular dysfunction. The authors concluded that this largest multi-center CMR study in ST-segment elevation myocardial infarction patients to date demonstrated no benefit of IC versus IV abciximab administration on myocardial damage and/or re-perfusion injury. Infarct size determined by CMR was significantly associated with major adverse cardiac events.

In a meta-analysis, Wang et al (2013) stated that abciximab is a widely used adjunctive therapy for acute coronary syndrome (ACS). However, the
Effect of IC administration of abciximab on cardiovascular events remains unclear when compared with IV therapy. These investigators systematically searched the Medline, Embase, and Cochrane Central Register of Controlled Trials databases and reference lists of articles and proceedings of major meetings for obtaining relevant literature. All eligible trials included ACS patients who received either IC administration of abciximab or IV therapy. The primary outcome was major cardiovascular events, and secondary outcomes included total mortality, re-infarction, and any possible adverse events. Of 660 identified studies, these researchers included 9 trials reporting data on 3,916 ACS patients. Overall, IC administration of abciximab resulted in 45% reduction in relative risk for major cardiovascular events (RR; 95% CI: 24 to 60%), 41% reduction in RR for re-infarction (95% CI: 7 to 63%), and 44% reduction in RR for congestive heart failure relative to IV therapy (95% CI: 8 to 66%); however, compared to IV therapy, IC administration of abciximab had no effect on total mortality (RR, 0.69; 95% CI: 0.45 to 1.07). No other significant differences were identified between the effect of IC abciximab administration and IV therapy. The authors concluded that IC administration of abciximab can reduce the risk of major cardiovascular events, re-infarction, and congestive heart failure when compared with IV therapy.

**Acute Limb Ischemia:**

Salzler et al (2016) stated that contemporary endovascular management of acute limb ischemia (ALI) generally consists of tissue plasminogen activator (tPA) based catheter-
directed thrombolysis (CDT) with or without pharmaco-mechanical thrombectomy (PMT). Although abciximab is widely used in coronary re-vascularization, its safety and effectiveness in the treatment of ALI are unknown. These investigators reviewed their contemporary experience with the endovascular management of ALI and evaluated the safety and effectiveness of abciximab. A total of 49 consecutive patients with Rutherford class II (RII) ALI undergoing CDT for ALI from 2011 to 2014 was identified.

Demographics, procedural details, and outcomes were assessed and reported. A total of 44 patients with RII ALI underwent tPA-based CDT in 49 discrete interventions. In 11 patients adjunctive abciximab infusion was also used. The majority (82%) of patients treated with tPA ± PMT required over-night infusion and at least 1 subsequent procedure. Single-stage (on-table) thrombolysis was achieved in 91% of cases with adjunctive abciximab use versus 18% with tPA alone (p < 0.001). There was significantly less need for intensive care unit (ICU) monitoring, and there were no bleeding complications associated with adjunctive abciximab use.

Overall length of stay and total operating room time favored the abciximab group; but did not reach statistical significance. Overall primary patency, secondary patency, and amputation-free survival were 46 ± 9.9%, 79 ± 6.6%, and 78 ± 9.2%, respectively, at 1 year. The authors concluded that early results suggested adjunctive abciximab may safely facilitate on-table thrombolysis for RII ALI. This approach appeared to be associated with reduced resource utilization including fewer procedures, shorter operating room time, and less ICU admissions and 1-year outcomes compared
favorably to a similar cohort of ALI patients treated with tPA-based therapy alone. These findings from a small study (only 11 subjects received abciximab) need to be validated in well-designed studies.

**Saphenous Vein Graft Interventions:**

Harskamp et al (2016) noted that PCI of saphenous vein grafts (SVG) poses a high-risk for distal coronary thrombo-embolic events. Glycoprotein IIb/IIIa inhibitors are frequently used in hope of reducing the impact of this, although the safety and effectiveness of these drugs to improve outcomes in this setting are under-studied. In this study, patients were included if they had prior coronary artery bypass surgery and subsequently underwent PCI of greater than or equal to 1 SVG graft at a Dutch academic center between 1997 and 2008. These patients were matched 1:1 based on peri-procedural use of abciximab using a propensity-score matching algorithm based on 17 variables. Conditional logistic regression and Cox regression stratified on matched pairs were performed to evaluate the association between abciximab use and MACCE (the composite measure of mortality, myocardial infarction, stroke and repeat revascularization) at 30 days and up to 1 year. The composite of 30-day MACCE occurred in 18 patients (15.3 %) in the abciximab group and 16 patients (13.6 %) in the propensity matched control group (OR: 1.13, 95 % CI: 0.57 to 2.21, p = 0.73). At 1-year follow-up, MACCE rates were also similar (32.5 % versus 33.9 %, HR: 0.97, 95 % CI: 0.59 to 1.59). Major bleeding (BARC types 3a-c) was higher in the abciximab group (11.9 % versus 4.2 %, OR: 2.80,
95% CI: 1.01 to 7.77). Ischemic outcomes did not differ among patients with ACS. The authors concluded that the use of intravenous abciximab was not associated with improved clinical outcomes up to 1-year among patients undergoing SVG PCI, but was related to more bleeding.

**Acute Ischemic Stroke:**

Al-Mufti and colleagues (2017) retrospectively delineated the feasibility of the combined use of emergent carotid stenting and intra-arterial (IA) abciximab with intracranial re-vascularization in the setting of acute ischemic stroke and carotid occlusions. A total of 11 patients with complete cervical carotid occlusion with or without concomitant intracranial ICA and/or MCA occlusion were identified from a single center, retrospective review of patients admitted to the Stroke unit. These researchers evaluated all cases for complications of emergent cervical ICA recanalization employing carotid stenting and IA abciximab. All patients had complete cervical carotid occlusion with (n = 8) or without (n = 3) concomitant intracranial ICA and/or MCA occlusion. Successful emergent cervical ICA recanalization was achieved in all cases. All patients were administered IA abciximab (dose range 6 to 17 mg, average of 11.4 mg) immediately following the cervical carotid stenting. There was complete re-canalization in all patients with no procedural morbidity or mortality. A single case (1/11, 9%) developed asymptomatic hemorrhagic transformation. Upon discharge, 9 patients (9/11, 82%) had a modified Rankin Scale (mRS) of 0 to 2, and 2 patients (2/11, 18%) had a mRS of 3. The
authors concluded that in acute ICA-MCA/distal ICA occlusions, extracranial stenting followed by intracranial IA abciximab and thrombectomy appeared feasible, safe, and effective. They stated that further evaluation of this treatment strategy is needed.

**Cardiac Complications (e.g., Coronary Artery Aneurysms) of Kawasaki Disease:**

Bachlava and co-workers (2016) stated that there are limited data regarding the possible benefits of abciximab in children with Kawasaki disease (KD), who developed serious cardiac abnormalities non-responsive to standard treatment. These investigators retrospectively identified children with KD who were treated with abciximab from 2007 to 2015. Data regarding clinical course, treatment, echocardiographic data and follow-up at 1 and 6 months were retrieved. During the study period, a total of 15 children were identified who were diagnosed with KD and were given abciximab. The median age at onset of symptoms was 11 months (range of 2 months to 6 years). The median day of disease at admission was 10 days (range of 4 to 26 days) and the median day of administration of abciximab was 17 days (range of 9 to 40 days); 12 children were diagnosed with complete and 3 with incomplete KD. Aneurysms were found in 8 children: 2 had ectatic coronary arteries and 5 presented with both ectasia and aneurysms. At 1 month follow-up, echocardiographic findings showed regression in the size of aneurysms in 11 children, resolution of the aneurysms or ectasia of coronary arteries in 3 children, while 1 child who could not take aspirin because of G6PD deficiency died. At 6
months of follow-up, echocardiographic findings showed resolution of coronary abnormalities in 12 (80 %) children, whereas 2 children (13.3 %) presented with significant regression of aneurysms. The authors concluded that abciximab may have an important role in the management of severe cardiac complications of KD, although prospective RCTs are needed to fully evaluate its role.

Thromboembolic Complications during Aneurysm Coiling:

Martínez-Perez and associates (2017) evaluated the safety and effectiveness of abciximab for the treatment of thromboembolic complications during aneurysm coiling and determined the risk factors. From an aneurysm coiling database, patients treated with intra-arterial abciximab after having thrombotic complications during the coiling procedure were selected for analysis. Complications after using abciximab were categorized as hemorrhage, distal migration of the thrombus, and aneurysm re-canalization. A total of 14 coiling patients sustained a thromboembolic complication and were treated using intra-arterial infusion of abciximab and were subjected to further analysis. The age range was 48 to 76 years; 3 patients were male; 7 had subarachnoid hemorrhage. Only complete re-canalization was associated with clinical improvement, but this only occurred in 4 (28.5 %) cases. Partial or complete re-canalization occurred in 13 (93 %); 8 (57 %) patients had complications derived from the infusion; 3 had aneurysm re-canalization, 3 had distal migration of the thrombus and 1 had a hemorrhagic complication; 8 cases
demonstrated acute infarcts related to the occluded vessel, while 7 made a good functional recovery. The authors concluded that successful re-canalization of a vessel occluded by thrombus formation during aneurysm coiling using abciximab infusion was less than optimal; there were risks related to abciximab, including bleeding and aneurysm re-canalization.

Abciximab for Thrombus Resolution During Intracranial Bypass Surgery:

Buchanan and colleagues (2018) noted that abciximab is a glycoprotein IIb/IIIa receptor antagonist that functions to prevent platelet aggregation, thus reducing thrombus initiation and propagation. The use of abciximab in cardiac and neurosurgical procedures has been associated with a reduced incidence of ischemic complications and a decreased need for repeated intervention. In these settings, abciximab has been delivered trans-arterially via a micro-catheter or infused intravenously for systemic administration. In a case-report, these investigators described novel in-situ delivery of abciximab as an agent to dissolve "white clots", which are composed primarily of platelets, during an intracranial superficial temporal artery to middle cerebral artery bypass in a 28-year old woman with severe intracranial occlusive disease. Abciximab was able to resolve multiple platelet-based clots after unsuccessful attempts with conventional clot dispersal techniques, such as heparinized saline, tPA, mechanical passage of a wire through the vessel lumen, and multiple take-downs and re-anastomosis. After abciximab was administered, patency was demonstrated intra-operatively using
indocyanine green (ICG) dye and confirmed post-operatively at 1 and 10 months via CT angiography. The authors concluded that the in-situ use of abciximab as an agent to disperse a thrombus during intracranial bypass surgery is novel and has not previously been described in the literature, and serves as an additional tool during intracranial vessel bypass surgery.

Abciximab/Heparin Therapy for Left Ventricular Assist Device Implantation in Patients with Heparin-Induced Thrombocytopenia:

Lee and associates (2018) stated that optimal anti-coagulation strategy remains uncertain in patients with heparin-induced thrombocytopenia (HIT) and undergoing left ventricular assist device (LVAD) implantation. These researchers described their protocol of abciximab and heparin in these patients. The protocol was to administer abciximab, 0.25 mg/kg loading dose, followed by continuous infusion of 0.125 μg · kg⁻¹ · min⁻¹ throughout cardio-pulmonary bypass. Full-dose heparin was then given with subsequent additional doses to maintain an activated clotting time of 400 seconds or longer. The abciximab infusion was stopped 15 minutes after heparin reversal with protamine, and platelets were transfused. A total of 6 patients underwent LVAD implantation with this protocol in the authors' program; HIT was confirmed in 4 patients; it was suspected in 2, which was negative after the operation; 1 patient received a HeartMate XVE and the others received HeartMate II. There were no thromboembolic complications; 1 patient required chest re-exploration for bleeding and temporary right VAD support. Post-operative
anti-coagulation with argatroban was re-started on median post-operative day 3 (range of days 1 to 6) and warfarin was started on day 5 (range of days 3 to 12). Median post-operative ICU stay was 9 days (range of 5 to 76), and hospital stay was 22 days (range of 18 to 132). After the initial LVAD implantation, 1 patient required HeartMate XVE LVAD exchange to HeartMate II and subsequent heart transplant, both of which were performed with the abciximab/heparin protocol. A HeartMate II device was explanted in another patient after myocardial recovery. The remaining 4 patients were alive on device support. The authors concluded that this was the first report of a novel abciximab/heparin protocol for LVAD implantation in patients with HIT. They stated that these preliminary findings suggested the feasibility and safety of this protocol. They stated that further studies in the use of this protocol in HIT patients requiring cardiac operations are needed.

The authors stated that this study had several drawbacks. First, this is a retrospective study, and the sample number was limited (n = 6). Second, there was no control group to compare the peri-operative outcomes. Moreover, there were 2 patients without serotonin release assay testing albeit with strong clinical evidence supporting the diagnosis of HIT.

### CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
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CPT codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 92974</td>
<td>Transcatheter placement of radiation delivery device for subsequent coronary intravascular brachytherapy (List separately in addition to code for primary procedure)</td>
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CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>61624</td>
<td>Transcatheter occlusion or embolization [e.g., for tumor destruction, to achieve hemostasis, to occlude a vascular malformation], percutaneous, any method; central nervous system [intracranial, spinal cord].</td>
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Other CPT codes related to the CPB:

<table>
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<th>Code</th>
<th>Description</th>
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<tr>
<td>33510 - 33516</td>
<td>Coronary artery bypass, vein only; 1-6 or more coronary venous grafts</td>
</tr>
<tr>
<td>96365 - 96368, 96374 - 96379</td>
<td>Intravenous infusion and push</td>
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</table>

HCPCS codes covered if selection criteria are met:

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<th>Code</th>
<th>Description</th>
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<tr>
<td>J0130</td>
<td>Injection abciximab, 10 mg [except for the management of acute myocardial infarction without percutaneous coronary intervention]</td>
</tr>
<tr>
<td>Q3001</td>
<td>Radioelements for brachytherapy, any type, each</td>
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</table>

Other HCPCS codes related to the CPB:

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C1874 - C1875</td>
<td>Stent, coated/covered, with or without delivery system</td>
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</tbody>
</table>

ICD-10 codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I20.0 - I25.3, I25.42 - I25.9</td>
<td>Ischemic heart diseases</td>
</tr>
<tr>
<td>T82.211+ - T82.218+</td>
<td>Mechanical complication due to coronary bypass graft</td>
</tr>
<tr>
<td>T82.817+, T82.827+, T82.837+, T82.847+, T82.857+, T82.867+, T82.897+, T82.9xx+</td>
<td>Other specified complications of other cardiac devices, implants and grafts</td>
</tr>
<tr>
<td>Z95.1</td>
<td>Presence of aortocoronary bypass graft</td>
</tr>
<tr>
<td>Z95.5</td>
<td>Presence of coronary angioplasty implant and graft</td>
</tr>
<tr>
<td>Z98.61</td>
<td>Coronary angioplasty status</td>
</tr>
<tr>
<td>ICD-10 codes not covered for indications listed in the CPB [not all-inclusive]:</td>
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<tr>
<td>I25.41</td>
<td>Coronary artery aneurysm</td>
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<tr>
<td>I63.00 - I66.9</td>
<td>Occlusion and stenosis of cerebral and precerebral arteries</td>
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<tr>
<td>I74.3</td>
<td>Embolism and thrombosis of arteries of the lower extremities</td>
</tr>
<tr>
<td>I99.9</td>
<td>Unspecified disorder of circulatory system [acute limb ischemia]</td>
</tr>
<tr>
<td>M30.03</td>
<td>Mucocutaneous lymph node syndrome</td>
</tr>
</tbody>
</table>

The above policy is based on the
following references:


52. U.S. Food and Drug Administration (FDA). 
ReoPro Abciximab for intravenous 
administration. Prescribing Information. 
Rockville, MD: FDA; 1997. Available at:  

53. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). 
Glycoprotein IIb/IIIa antagonists: A systematic review of randomized clinical 
trials in patients undergoing percutaneous coronary intervention. Technology Report 
No. 49. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment 
(CCOHTA); January 2005:1-72.

Economic evaluation of glycoprotein IIb/IIIa 


82. Prati F, Romagnoli E, Limbruno U, et al. Randomized evaluation of intralesion versus


89. Lee CL, Colombo PC, Eisenberger A, et al. Abciximab/heparin therapy for left ventricular assist device implantation in

AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number:
0491 Coronary Artery Brachytherapy and Other Adjuncts to Coronary Interventions

There are no amendments for Medicaid.