CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will interpret the evidence for and against measuring troponin levels in noncardiac postoperative patients

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Troponin elevation after noncardiac surgery: Significance and management

ABSTRACT

How to interpret and manage troponin elevations after noncardiac surgery is a common clinical question for cardiologists and internists. An estimated 5% to 25% of patients who undergo noncardiac surgery have an elevated postoperative troponin level. Patients with troponin elevation are at higher short-term and long-term risk of morbidity and mortality. Current guidelines provide few recommendations on how to manage these patients. The authors review the evidence and guidelines and propose treatment strategies.

KEY POINTS

Cardiovascular events are a major cause of morbidity and mortality in patients undergoing noncardiac surgery and occur frequently, especially in high-risk patients.

Myocardial injury or infarction after noncardiac surgery heightens the short- and long-term risk of mortality and major adverse cardiac events.

The dominant mechanism of myocardial injury after noncardiac surgery remains uncertain.

In the absence of therapies proven to affect the outcome, the benefit of screening to identify these patients remains uncertain.

Clinical trials are under way to help clinicians provide optimal care to this at-risk population.

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More than 200 million patients undergo noncardiac surgery each year, and the volume is increasing.[1] Cardiovascular complications are a major cause of morbidity and mortality in the perioperative period.

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Before the advent of modern cardiac biomarkers, an estimated 2% to 3% of all patients undergoing noncardiac surgery had a major adverse cardiac event.[2] However, more recent studies suggest that 5% to 25% of patients have troponin elevations after noncardiac surgery, depending on the patient population,[3–6] and many are asymptomatic, suggesting that many patients are sustaining undetected myocardial injury. Those who suffer a myocardial infarction or myocardial injury have elevated morbidity and mortality rates, not only perioperatively, but also at 30 days and even at up to 1 year.[3–5,7–11]

Yet there are almost no data on how best to manage these patients; the available guidelines, therefore, do not provide sufficient recommendations for clinical practice.

To address the lack of guidelines, we examine the incidence and proposed mechanisms of myocardial injury after noncardiac surgery, suggest an approach to identifying patients at risk, recommend treatment strategies, and consider future directions.

CARDIAC BIOMARKERS

When cardiac cellular injury from ischemia, direct trauma, or other cause disrupts the cell membrane, intracellular contents enter

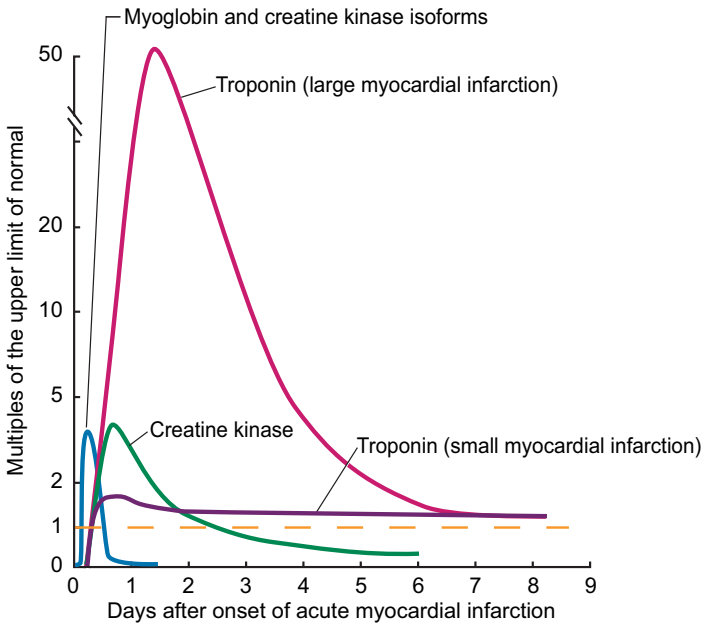

FIGURE 1. Time of release of selected cardiac biomarkers after myocardial infarction.

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Troponin assays are not standardized, so levels from different laboratories cannot be compared

the extracellular space, including the blood stream. If the myocyte damage is extensive enough, biochemical assays can detect these substances.

Troponin, creatine kinase, myoglobin, and lactate dehydrogenase are common biomarkers of necrosis that, when detected in the plasma, may indicate cardiac injury. Each can be detected at varying times after cardiac injury (**Figure 1**).[12]

Cardiac troponins I and T

Of the biomarkers, cardiac troponin I and cardiac troponin T are now the most widely used and are the most specific for myocyte injury.

Troponins are proteins that regulate the calcium-induced interaction between myosin and actin that results in muscle contraction. Troponin is a complex consisting of three subunits: troponin C, troponin I, and troponin T. The cardiac troponin I and T isoforms are distinct from those found in skeletal muscle, making them specific for myocyte injury, and they are currently the recommended markers for diagnosing acute myocardial infarction.[13]

The troponin immunoassays currently available are not standardized among laboratories and point-of-care methods, and thus, levels cannot be compared across testing centers.[14] Each assay has unique performance characteristics, but guidelines recommend using the 99th percentile value from a normal reference population for a given assay to define whether myocardial injury is present.[13]

Troponin elevation has prognostic value in patients presenting with acute coronary syndromes,[15–18] and the degree of elevation correlates with infarct size.[19–21]

Controversy exists as to whether troponin and other biomarkers are released only after myocardial necrosis or after reversible injury as well. Using newer, highly sensitive assays, troponin elevations have been detected after short periods of ischemia during stress testing[22,23] and in patients with stable angina,[24] suggesting that reversible cardiac stress and injury can lead to troponin release. This mechanism may play an important role during the myocardial injury that can occur in patients undergoing noncardiac surgery.

MYOCARDIAL INFARCTION VS MYOCARDIAL INJURY

In 2000, the Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and World Heart Federation revised the criteria for the diagnosis of myocardial infarction created by the World Health Organization in 1979. The definition was revised again in 2007 and once more in 2012 to create the third universal definition of myocardial infarction.

Acute myocardial infarction

Acute myocardial infarction is defined as evidence of myocardial necrosis in a setting of myocardial ischemia, not related to causes such as trauma or pulmonary embolism, with a rise or a fall (or a rise *and* a fall) of cardiac biomarkers (at least one value being above the 99th percentile in the reference population) and any of the following:

- Symptoms of ischemia
- New ST-segment changes or new left bundle branch block
- Pathologic Q waves
- Imaging evidence of new loss of viable

myocardium or new regional wall-motion abnormality
- Intracoronary thrombus by angiography or autopsy.[13]

Myocardial injury after noncardiac surgery

Studies[10,11] have shown that many patients undergoing noncardiac surgery have evidence of cardiac biomarker release but do not meet the universal definition of myocardial infarction.

The Perioperative Ischemic Evaluation (POISE) trial[10] reported that 415 (5%) of its patients met the definition of myocardial infarction, of whom only about 35% had symptoms of ischemia. Another 697 patients (8.3%) had isolated elevations in biomarkers without meeting the definition of myocardial infarction.

The VISION study[11] (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation) prospectively screened more than 15,000 patients in several countries for troponin elevation during the first 3 postoperative days and for ischemic symptoms and features. Of the patients screened, approximately 1,200 (8%) had troponin elevations, with fewer than half fulfilling the criteria for myocardial infarction.

In another study, van Waes et al[6] prospectively screened 2,232 patients ages 60 and older undergoing intermediate- to high-risk noncardiac surgery. Troponin levels were elevated in 19% of the patients, but only 10 of these patients met the universal definition of myocardial infarction.

In all of these studies, patients with isolated elevation in myocardial biomarkers had worse short-term and long-term outcomes than those without. These observations led to a proposed definition of "myocardial injury after noncardiac surgery" that is broader than that of myocardial infarction and requires only elevation of cardiac biomarkers judged to be due to myocardial ischemia (ie, not from another obvious cause such as pulmonary embolism or myocarditis).[3]

FIVE TYPES OF MYOCARDIAL INFARCTION

The Joint Task Force[13] categorizes myocardial infarction into five distinct types:
- Type 1—due to plaque rupture
- Type 2—due to imbalance between oxygen supply and demand
- Type 3—sudden cardiac death
- Type 4a—associated with percutaneous coronary intervention
- Type 4b—associated with stent thrombosis
- Type 5—associated with coronary artery bypass surgery.

Types 1 and 2 have both been implicated in perioperative myocardial infarction and injury. Patient characteristics and the physiologic response to surgical and anesthetic stressors likely contribute to the development of myocardial infarction and injury after noncardiac surgery.

Plaque rupture as a cause of postoperative myocardial infarction

The mechanism of type 1 myocardial infarction—plaque rupture or erosion leading to thrombosis and infarction—plays a significant role in most cases of acute coronary syndromes. Its role in perioperative and postoperative myocardial infarction or injury, however, is less clear.

In an autopsy study of 26 patients who died of myocardial infarction after noncardiac surgery, plaque rupture was evident in 12 (46%).[25] A prospective angiographic study of 120 patients with acute coronary syndromes after noncardiac surgery found that nearly 50% had evidence of plaque rupture.[26]

Is troponin released only after necrosis, or also after reversible injury?

Higher levels of catecholamines, cortisol,[27,28] platelet reactivity,[29] procoagulant factors,[30] and coronary artery shear stress[31] are all present in the postoperative period and may contribute to an increased propensity for plaque rupture or erosion. Whether plaque rupture is present in patients who have isolated troponin elevation but do not meet the criteria for myocardial infarction has not been investigated.

Oxygen supply-demand imbalance during and after surgery

Oxygen supply-demand imbalance (the mechanism in type 2 myocardial infarction) leading to myocyte stress, ischemia, and subsequent infarction is likely common in the perioperative and postoperative periods. As previously discussed, this imbalance may be present with or without symptoms.

Oxygen demand may increase in this period as a result of tachycardia[32] caused by bleeding, pain, and catecholamines or in-

creased wall stress from hypertension due to vasoconstriction or pain.[33] Oxygen supply can be decreased secondary to tachycardia, anemia,[34] hypotension, hypoxemia, hypercarbia, intravascular fluid shifts (bleeding or volume overload), or coronary vasoconstriction.[33,35]

These mechanisms of myocardial injury, infarction, or both can occur with or without underlying significant obstructive coronary artery disease. However, severe coronary artery disease is more common in those who have had a perioperative myocardial infarction.[36]

POSTOPERATIVE TROPONIN ELEVATION CARRIES A WORSE PROGNOSIS

Patients who suffer a myocardial infarction after noncardiac surgery have worse short- and long-term outcomes than their counterparts.[4,5,7,8,10,33] In the POISE trial,[10] the 30-day mortality rate was 11.6% in those who had had a perioperative myocardial infarction, compared with 2.2% in those who did not ($P < .001$). The patients who had had a myocardial infarction were also more likely to have nonfatal cardiac arrest, coronary revascularization, and congestive heart failure.

'Myocardial injury after noncardiac surgery' requires only troponin elevation for diagnosis

Myocardial injury not fulfilling the criteria for myocardial infarction after noncardiac surgery is also associated with worse short-term and long-term outcomes.[3,6,10,11,37,38] POISE patients with isolated elevations in cardiac biomarkers had a higher 30-day risk of coronary revascularization and nonfatal arrest.[10] In the VISION trial, an elevation in troponin was the strongest predictor of death within 30 days after noncardiac surgery. This analysis also showed that the higher the peak troponin value, the greater the risk of death and the shorter the median time until death.[11]

A meta-analysis of 14 studies in 3,139 patients found that elevated troponin after noncardiac surgery was an independent predictor of death within 1 year (odds ratio [OR] 6.7, 95% confidence interval [CI] 4.1–10.9) and beyond 1 year (OR 1.8, 95% CI 1.4–2.3).[37]

SHOULD SCREENING BE ROUTINE AFTER NONCARDIAC SURGERY?

Since patients suffering myocardial infarction or injury after noncardiac surgery have a worse prognosis, many experts advocate routinely screening all high-risk patients and those undergoing moderate- to high-risk surgery. Many tools exist to determine which patients undergoing noncardiac surgery are at high risk of cardiac complications.

The revised Goldman Cardiac Risk Index is commonly used and well validated. Variables in this index that predict major cardiac complications are:

- High-risk surgery (vascular surgery, orthopedic surgery, and intraperitoneal or intrathoracic surgery)
- History of ischemic heart disease
- History of congestive heart failure
- History of cerebrovascular disease
- Diabetes requiring insulin therapy
- Chronic kidney disease with a creatinine > 2.0 mg/dL.

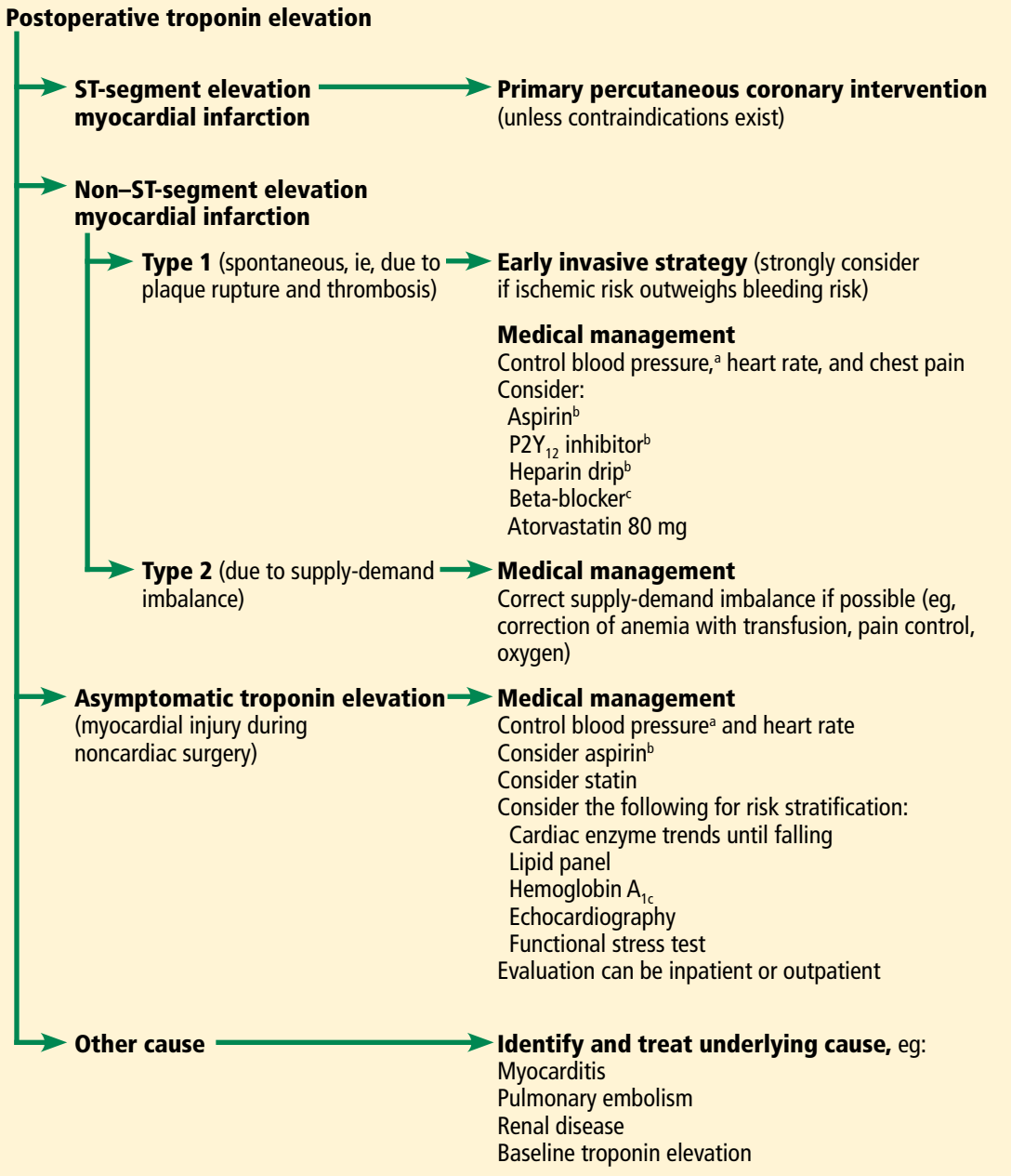
The more of these variables that are present, the higher the risk of perioperative cardiac events[2,4]:

- No risk factors: 0.4% risk (95% CI 0.1–0.8)
- One risk factor: 1.0% risk (95% CI 0.5–1.4)
- Two risk factors: 2.4% risk (95% CI 1.3–3.5)
- Three or more risk factors: 5.4% risk (95% CI 2.7–7.9).

Current guidelines from the American College of Cardiology and the American Heart Association give a class I recommendation (the highest) for measuring troponin levels after noncardiac surgery in patients who have symptoms or signs suggesting myocardial ischemia. They give a class IIb recommendation (usefulness is less well established) for screening those at high risk but without symptoms or signs of ischemia, despite the previously cited evidence that patients with troponin elevation are at increased risk. The IIb recommendation is due to a lack of validated treatment strategies to modify and attenuate the recognized risk with troponin elevation in this setting.[39]

LITTLE EVIDENCE TO GUIDE TREATMENT

In current practice, internists and cardiologists are often asked to consult on patients with troponin elevations noted after noncardiac surgery. Although published and ongoing studies examine strategies to prevent cardiovascular events *during* noncardiac surgery, we lack data on managing the cases of myocardial



[a]Goal blood pressure should be 110–140/70–90 mm Hg.
[b]Consider only if ischemic risk outweighs bleeding risk; decision should be made jointly with surgeon.
[c]Goal heart rate 50–70 beats per minute, if blood pressure is tolerated, and there is no concern for depressed left ventricular ejection fraction or cardiogenic shock.

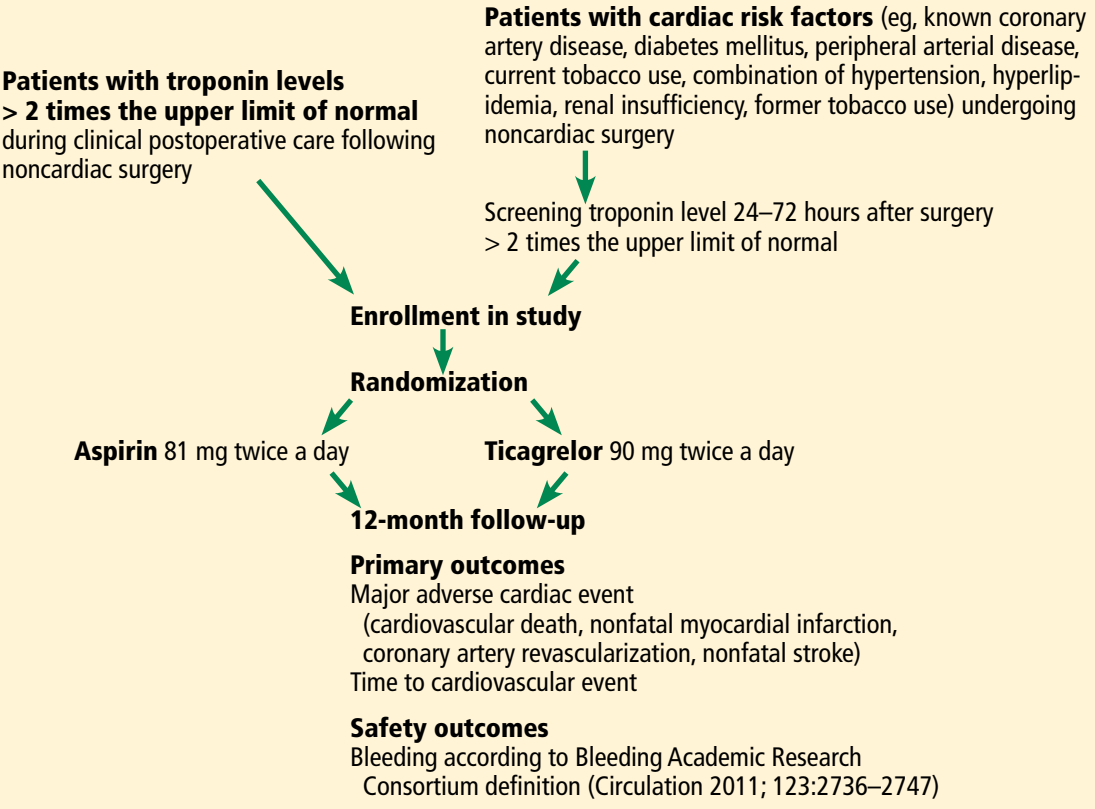
FIGURE 2. Proposed treatment algorithm for patients with postoperative troponin elevation after noncardiac surgery.

Ultimately, treatment decisions should be tailored to the individual patient

infarction and injury that actually occur *after* noncardiac surgery.

When managing a patient who has a troponin elevation after surgery, many clinical factors must be weighed, including hemodynamic and clinical stability and risk of bleeding. Confronted with ST-segment elevation myocardial infarction or high-risk non–ST-segment elevation myocardial infarction, most clinicians would favor an early invasive

INTREPID study design



INTREPID: Study of Ticagrelor Versus Aspirin Treatment in Patients With Myocardial Injury Post Major Non-Cardiac Surgery (ClinicalTrial.gov Identifier NCT02291419).

FIGURE 3

INTREPID will enroll about 1,000 patients with troponin levels > 2 times the upper limit of normal

reperfusion strategy in accordance with guidelines on managing acute coronary syndrome. Fibrinolytic drugs for ST-segment elevation myocardial infarction are likely to be contraindicated in the postoperative period because they pose an unacceptable risk of bleeding.

Guideline-directed medical therapies for those suffering perioperative myocardial infarction may lower the risk of future cardiovascular events, as suggested by a retrospective study of 66 patients diagnosed with perioperative myocardial infarction after vascular surgery.[40] Those in whom medical therapy for coronary artery disease was not intensified—defined as adding or increasing the dose of antiplatelet agent, statin, beta-blocker, or angiotensin-converting enzyme inhibitor—had higher rates of cardiovascular events at 12 months (hazard ratio [HR] 2.80, 95% CI 1.05–24.2).[40]

In those with asymptomatic myocardial infarction or isolated elevation in cardiac biomarkers, no treatment strategies have been assessed prospectively or in randomized trials. However, statins and aspirin have been suggested as providing some benefit. In a substudy of the POISE trial, the use of aspirin was associated with a 46% reduction in the 30-day mortality rate in those suffering a perioperative myocardial infarction, and statins were associated with a 76% reduction.[10] In a single-center retrospective analysis of 337 patients undergoing moderate- to high-risk vascular surgery, statin therapy was associated with a lower 1-year mortality rate (OR 0.63, 95% CI 0.40–0.98).[38]

We propose a treatment algorithm for patients identified as having cardiovascular events after noncardiac surgery (**Figure 2**), based on current evidence and guidelines. Ultimately, treatment decisions should be tailored to the individual patient. Discussion of the risks and benefits of therapeutic options should include the patient and surgeon.

Ongoing and future trials

Ongoing and future trials are aimed at addressing definitive treatment strategies in this patient population.

The MANAGE trial (Management of Myocardial Injury After Non-cardiac Surgery Trial) is randomizing patients suffering myocardial injury after noncardiac surgery to receive either dabigatran and omeprazole or placebo to assess the efficacy of these agents in preventing major adverse cardiac events and the safety of anticoagulation (ClinicalTrials.gov Identifier: NCT01661101).

The INTREPID trial (Study of Ticagrelor Versus Aspirin Treatment in Patients With Myocardial Injury Post Major Non-Cardiac Surgery) will assess the efficacy and safety of ticagrelor treatment compared with aspirin in a similar population (ClinicalTrial.gov Identifier: NCT02291419). The trial will enroll approximately 1,000 patients identified as having a postoperative troponin elevation more than two times the upper limit of normal of the assay during the index hospitalization (**Figure 3**). Enrollment was to have begun in mid-2015.

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