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Internal Medicine

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Vol. 37, Issue 4, February 28, 2015
www.ahcmedia.com

Should Clinicians Discuss Resumption of Sexual Activity Following an Acute MI?

Jeff Unger, MD, ABFM, FACE

SYNOPSIS: Although the U.S. and European cardiovascular society guidelines recommend that patients be counseled about resuming sexual activity after suffering an acute myocardial infarction (AMI), the actual demographics of sexual education post-myocardial infarction (MI) are unknown. The prospective, longitudinal Variation in Recover: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study evaluated the gender differences in baseline and sexual activity, function, and patient experience with physician counseling following acute MI. Among the 2349 women and 1152 men interviewed, only 12% of women and 19% of men reported discussing sexual activity with a physician within a month following AMI. Women received more restrictions than men, few of which were supported by evidence or guidelines.

SOURCE: Lindau ST, et al. Sexual activity and counseling in the first month after acute myocardial infarction (AMI) among younger adults in the United States and Spain: A prospective, observational study. *Circulation* 2014. Dec 15. DOI: 10:161/circulationAHA.114.012709.

Acute myocardial infarction (AMI) can result in reduced sexual activity and function, as patients may fear that sexual intercourse may trigger another fatal event. Loss of sexual activity following AMI can increase one's risk of major depression, resulting in strained relationships and diminished quality of life. Childbearing potential may be affected in younger patients. Lack of understanding of sexuality post-MI can compromise adherence to medical care and is associated with poorer overall outcomes.

The risk of coital death is rare, with only 0.6% of sudden deaths attributable to sexual intercourse. Less than 1% of all MIs occur during sexual activity. Although sexual activity can trigger MI, the relative risk is low, with a slight increase in risk within 2 hours of sexual activity. Even in high-risk individuals with previous MI, the annual risk is 1.10% vs 1.0% in the population at large. This risk appears to apply equally to men and women.

Sexual intercourse can be related to performing moderate physical activity, similar to walking, lifting, and light housework. Heart rates rarely exceed 130 beats/min, and systolic blood pressures are generally

Financial Disclosure: *Internal Medicine Alert*'s editor, Stephen Brunton, MD, is a retained consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Meda Pharmaceuticals, Novartis, Novo Nordisk, Sanofi, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Leslie Hamlin report no financial relationships relevant to this field of study.

[INSIDE]

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Internal Medicine Alert,
ISSN 0195-315X, is published monthly by
AHC Media, LLC
One Atlanta Plaza,
950 East Paces Ferry Road NE, Suite 2850
Atlanta, GA 30326.
www.ahcmedia.com

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Internal Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

SUBSCRIBER INFORMATION
1-800-688-2421
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Subscription Prices
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less than 170 mmHg. However, there is some individual variation, based on age and general physical conditioning, with some patients attaining heart rates up to 180 beats/min with orgasm. Patients with known coronary artery disease may develop malignant arrhythmias during intercourse.

■ COMMENTARY

Clinicians should take the time to stratify their post-MI patients as being low or high risk. Patients who have stable angina, no evidence of congestive heart failure, stable blood pressure, and are adherent to their prescribed drug regimen may begin sexual activity 1 week following their acute event. The American Heart Association published guidelines for resumption of sexual activity following AMI are noted in *Table 1*. High-risk patients should undergo stress testing prior to approving their return to sexual activity. Patients with symptomatic valvular heart disease should delay sexual activity until their medical condition is stabilized and optimally managed. ■

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Table 1. Sexual Activity And Cardiovascular Disease (CVD) : General Recommendations

1. Women with CVD should be counseled regarding the safety and advisability of contraceptive methods and pregnancy when appropriate.
2. It is reasonable that patients with CVD wishing to initiate or resume sexual activity be evaluated with a thorough medical history and physical examination.
3. Sexual activity is reasonable for patients with CVD who, on clinical evaluation, are determined to be at low risk of cardiovascular complications.
4. Exercise stress testing is reasonable for patients who are not at low cardiovascular risk to assess exercise capacity and development of symptoms, ischemia, or arrhythmias.
5. Sexual activity is reasonable for patients who can exercise > 3-5 METS without angina, excessive dyspnea, ischemic ST-segment changes, cyanosis, hypotension, or arrhythmia.
6. Cardiac rehabilitation and regular exercise can be useful to reduce the risk of cardiovascular complications with sexual activity for patients with CVD.
7. Patients with unstable, decompensated, and/or severe symptomatic CVD should defer sexual activity until their condition is stabilized and optimally managed.
8. Patients with CVD who experience cardiovascular symptoms precipitated by sexual activity should defer sexual intercourse until their condition is stabilized and optimally managed.
Reference: Levine GN, et al. Sexual activity and cardiovascular disease. A scientific statement from the American Heart Association. *Circulation* 2012;125:1058-1072.

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Treatment of *C. Difficile* — Follow the Guidelines

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

This article originally appeared in the February 2015 issue of *Infectious Disease Alert*.

SYNOPSIS: Treatment based on the IDSA guidelines appears to improve outcomes, with a lower risk of relapse, surgery, and death, and should be broadly implemented.

SOURCE: Brown AT, et al. Effect of treatment variation on outcomes in patients with *Clostridium difficile*. *Am J Med* 2014;127:865-870.

Formal recommendations for the treatment of *C. difficile* infection (CDI), based on expert opinion and available literature, were published by the Infectious Disease Society of America (IDSA) in 2010.[1] These authors performed a retrospective study for 6 months in 2011, evaluating the effectiveness of the IDSA guideline-directed CDI treatment compared with alternate treatment at their tertiary care county teaching hospital. IDSA recommendations for CDI treatment are included in Table 1. Patients with CDI were identified based on ICD-9 coding at discharge and treatment for CDI infection. Demographic information was collected, and patients were classified as mild-to-moderate, severe, or severe-complicated based on the IDSA guidelines. The primary outcome of the study was the occurrence of complications, including relapse within 4 weeks, surgery, toxic megacolon, and 30-day mortality. Secondary outcomes included length of stay and clinical cure.

A total of 180 adults with CDI met criteria for inclusion in the study, 93 of whom (52%) were treated in accordance with the IDSA guidelines. The two groups (guideline-directed care and alternate care) were similar with respect to race and classification of disease severity, although those who received alternate care tended to be older and were more likely male. Only 116 (64%) of the participants had received antibiotics within the previous 8 weeks. In these subjects, antibacterials were used for an average of 8

Clinical Definition	Supportive Clinical Data	Recommended Treatment	Strength of Recommendation
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/μL or lower and a serum creatinine level < 1.5 times the premorbid level	Metronidazole, 500 mg 3 times per day by mouth for 10-14 days	A-I
Initial episode, severe	Leukocytosis with a white blood cell count of 15,000 cells/μL or higher or a serum creatinine level ≥ 1.5 times the premorbid level	Vancomycin, 125 mg 4 times per day by mouth for 10-14 days	B-I
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin.	C-III
First recurrence	—	Same as for initial episode	A-II
Second recurrence	—	Vancomycin in a tapered or pulsed regimen	B-III

Reprinted with permission from: Cohen SH, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;31:431-455.

days ± 10 days. Quinolones were received more often (32%) than other agents. In addition, proton pump therapy was administered within the previous 8 weeks to 100 patients (55%).

The NAP-1 strain was identified in 37% of the group receiving guideline-directed care, compared with 41.4% of the group receiving alternate care (P = NS), although was more frequently identified in patients with severe/complicated infection. Patients with the NAP-1 strain had a higher rate of ICU admission and significantly higher risk of mortality.

Guideline-directed care was associated with significantly fewer complications than alternate care (17.2% vs 56.3%; $P < .0001$). This was due in large part to a lower rate of mortality in persons receiving guideline-directed care compared with those in the alternate therapy group (5% vs 21.8%, $P = 0.0012$), as well as a lower rate of recurrence (14% vs 35.6%, $P = 0.0007$). Clinical cures were more frequent in patients receiving guideline-directed care compared with alternate care (93.5% vs 71.3%). Multiple logistical regression analysis demonstrated that relapses were 72% less likely in patients receiving guideline-directed care compared with alternate care.

Guideline-directed care was more often used in patients with mild-to-moderate disease (81%) compared with those with severe disease (35%) or those with severe-complicated disease (19.7%). The main reasons for patients with severe disease not meeting criteria for guideline-directed care included the use of flagyl as a single agent (55%) and failure to receive a taper or pulse therapy in those with multiple recurrences (23%). The main reasons for patients with severe-complicated disease not meeting criteria for guideline-directed care were the use of flagyl as single agent (57%) and the use of oral vancomycin without parenterally administered flagyl (35%).
In conclusion, many of the patients with CDI in this study were initially treated with flagyl — regardless of their disease classification — which meant those with mild-to-moderate disease met the guidelines (and did well), while many of those with more severe disease received inadequate therapy with flagyl or vancomycin alone, with a resulting increased risk of complications and mortality.

■ COMMENTARY

Treatment based on the IDSA guidelines appears to improve outcomes, with a lower risk of relapse, surgery, and death, and should be broadly implemented. Teaching hospitals, in particular, have a responsibility to train and educate their house staff about the use of currently recommended therapies. ■

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The Economic Burden of Undiagnosed Pre-diabetes … A Call for Action

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SYNOPSIS: The economic burden of diagnosed and undiagnosed diabetes, gestational diabetes, and prediabetes exceeded $322 billion in 2012. The excess cost consists of $244 billion in excess medical expenditures and $78 billion in reduced productivity. This amounts to an economic burden exceeding $1000 for each American in 2012. Costs for diabetes care have increased 48% since 2007 ($218 billion).

SOURCE: Dall TM, et al. The economic burden of elevated blood glucose levels in 2012. Diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes. *Diabetes Care* 2014;37:3172-3179.

The American Diabetes Association reported in 2013 that diagnosed diabetes accounts for 10% of the total health care expenditures ($245 billion) in the United States. This study by Dall et al suggests that the cost of dysglycemia is much larger when one factors in expenses related to gestational diabetes, undiagnosed diabetes, and prediabetes. Although costs of individualized diabetes care have risen less than the per capita cost of national health care expenditures (19% vs 24%) from 2007-

2012, increased prevalence of dysglycemia, rather than higher costs incurred per patient, is driving the economic burden of diabetes care in the United States. Gregg et al stated that the incidence of myocardial infarctions in patients with diabetes has declined 67% from 1990-2010, with stroke and amputation rates decreasing 53% and 52%, respectively.[1]

Reduction rates in these complications were higher among adults with diabetes than among age-matched individuals with normal glucose tolerance. This is excellent news for insurance executives who must pay for long-term complications. However, 86 million Americans have prediabetes, an increase of 7 million people since 2010. Thirty percent of these patients are expected to convert to clinical diabetes within the next 10 years, and by 2030, 30% of the adult U.S. population will be living with diabetes.

The economic burden associated with prediabetes is on the rise. From 2007-2012, the cost of managing patients with prediabetes in the United States has increased 74% from $33-$44 billion.[2-5] Unless low-cost diabetes prevention efforts (lifestyle intervention, increased activity, and weight loss) are initiated, the economic burden of managing more patients with diabetes will be unsustainable for our health care system.

■ COMMENTARY

Screening high-risk patients for pre-diabetes is cost-effective and advisable. By spending less than $200 per high-risk screening, those patients who are diagnosed with prediabetes can be treated intensively with lifestyle interventions and, if appropriate, metformin. Such non-invasive therapies will result in a per-quality adjusted life-year gained savings for screened individuals of more than $8000.

Our goal as clinicians should be to identify high-risk patients. Once dysglycemia is diagnosed, our strategy should be to achieve the targeted lipid, glycemic, and blood pressure goals as soon as possible. We should then maintain these targets for as long as possible, as safely as possible, and as rationally as possible. ■

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PHARMACOLOGY UPDATE

Edoxaban Tablets (Savaysa™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

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The third oral factor Xa inhibitor has been approved by the FDA. Edoxaban is the fourth target-specific oral anticoagulant (TSOA) to enter the market following dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis). Edoxaban is manufactured by Tokyo-based Daiichi Sankyo Company and marketed by Daiichi Sankyo as Savaysa.

INDICATIONS

Edoxaban is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF), as well as for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) after initial treatment with a parenteral anticoagulant.[1]

DOSAGE

The recommended dose for NVAF and DVT/PE is 60 mg daily.[1] The dose should be reduced to 30 mg daily in NVAF patients with a CrCl 15-50 mL/min. For DVT/PE, the dose should be reduced to 30 mg if CrCl is 15-50 mL/min, body weight is ≤ 60 kg, or the patient is using certain P-gp inhibitors (e.g., ketoconazole, quinidine, erythromycin, cyclosporine).

POTENTIAL ADVANTAGES

Edoxaban is the second TSOA to offer once-a-day dosing, along with rivaroxaban.

POTENTIAL DISADVANTAGES

There is reduced efficacy in patient with creatinine clearance > 95 mL/min.[1] Premature discontinuation of edoxaban increases the risk of ischemic events.[1] For the acute treatment of DVT/PE, edoxaban (and dabigatran) requires parenteral therapy prior to their initiation. Co-administration with strong P-gp inducers, such as rifampin, should be avoided.

COMMENT

The efficacy and safety of edoxaban were evaluated in two large clinical trials with warfarin as the active control. These were the ENGAGE AF-TIMI 48 study for NVAF (n = 21,105) and the Hokusai-VTE (venous thromboembolism) for DVT/AF (n = 8241).[1-3] In the first study, NVAF subjects were randomized to 30 mg edoxaban or 60 mg warfarin. Subjects on warfarin maintained a mean time in therapeutic range (TTR) of the international normalized ratio of 2.0-3.0 to 65%. Subjects were randomized to edoxaban 60 mg, 30 mg, or warfarin. The primary endpoint was first stroke (ischemic or hemorrhagic). The primary analysis was a modified intention-to-treat during on-treatment or within 3 days of the last dose taken. After a median follow-up of 2.8 years, edoxaban 60 mg had a lower incidence of stroke (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.65-0.98). The 60 mg dose was not superior to warfarin. The 30 mg dose was inferior to warfarin.

In a secondary analysis, in all patients randomized during the study period, the incidence of stroke was similar: 1.49% (high-dose edoxaban) compared to 1.69% (warfarin). Intracranial hemorrhages were significantly lower for both doses of edoxaban compared to warfarin. Major bleeding overall was lower with edoxaban, but GI bleeding was higher (HR, 1.40; 95% CI, 1.13-1.73). Subjects who were naïve to vitamin K antagonists fared better than those who were treatment-experienced. Those with CrCl > 95 mL/min had poorer outcomes. For DVT/PE, 4921 subjects with DVT and 3319 with PE were randomized to edoxaban 60 mg (30 mg in those with CrCl 30-50 mL/min) or warfarin. All subjects had received treatment with heparin or low molecular weight heparin for at least 5 days. The primary efficacy endpoint was recurrent symptomatic venous thromboembolism, and the primary safety outcome was major or clinically relevant non-major bleeding. Edoxaban was non-inferior to warfarin in terms of efficacy but superior to warfarin in terms of safety outcome.

CLINICAL IMPLICATIONS

Edoxaban enters the market as the third anti-Xa inhibitor and the fourth TSOA. Previously approved TSOAs include the Xa inhibitors rivaroxaban (Xarelto) and apixaban (Eliquis) and the direct thrombin inhibitor dabigatran (Pradaxa). There are currently no published studies among these agents. In a comparative analysis and meta-analysis of major clinical trials in atrial fibrillation with apixaban, edoxaban, rivaroxaban, and warfarin, major bleeding was lower with apixaban and edoxaban compared with warfarin, but not with rivaroxaban.[4] In another indirect comparison, edoxaban was not significantly different compared to apixaban in terms of efficacy endpoints, mortality, myocardial infarction, and major bleeding.[5]

Dabigatran (150 mg twice daily) was associated with lower stroke and systemic embolism compared to edoxaban. For indirect comparison in acute venous thrombosis, there appears to be no difference in recurrent VTE or all-cause mortality among the four agents,[6] although edoxaban was associated with a higher risk of major bleeding compared to apixaban. Being the newest agent approved, its role is yet to be determined. Current ACC/AHA/HRS guidelines recommend the thrombin inhibitor (dabigatran) or a factor Xa inhibitor (rivaroxaban or apixaban) in patients with NVAF unable to maintain a therapeutic INR level with warfarin.[7] The recommended treatment for acute DVT or PE is initial parenteral anticoagulation (e.g., low molecular weight heparin), followed by warfarin, dabigatran, apixaban, or edoxaban. Rivaroxaban, however, does not require initial therapy with heparin.[8] The wholesale monthly cost for edoxaban is $277, compared to $315 for dabigatran, rivaroxaban, and apixaban. ■

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Clinical Briefs

By Louis Kuritzky, MD

Metformin: Have we Been Overcautious in CKD?

SOURCE: Inzucchi SE, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014;312: 2668-2675.

Boundaries devised by regulatory agencies around the world for safe use of metformin differ from FDA labelling in the United States. Many other nations allow more liberal use of metformin, indicating it as safe at lower levels of renal function than the boundaries physicians are used to: creatinine ≥ 1.5 md/dL for men, ≥ 1.4 mg/dL for women, or an eGFR < 60 mL/min/1.73 m^2. The observation that metformin has been used in patients with chronic kidney disease (CKD) beyond these boundaries safely, and the relative rarity of lactic acidosis related to metformin in the United States, has stimulated a reappraisal of the recommendations for patients with CKD. Metformin is cleared by the kidneys, but the original dosing and safety recommendations put into place more than 20 years ago are reportedly based on potential administration of metformin at doses up to 3g/d, which, of course, is substantially above the usual maximum dose actually used in the United States (2000-2550 mg/d).

Inzucchi et al reviewed the literature in reference to studies that evaluated metformin, kidney disease, and lactic acidosis. Several trials even included plasma metformin measured at eGFR levels as low as < 30 mL/min. The authors opine that — contingent on regular monitoring — metformin might be safely used in diabetics with CKD down to an eGFR as low as 30 mL/min. ■

Reduction in Prostate Cancer Mortality with Screening

SOURCE: Schroder FH, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet* 2014;384: 2027-2035.

The pendulum swing in enthusiasm for prostate cancer screening from strong endorsement to disenchantment resulted from a huge clinical trial database of two mega trials that enrolled more than 250,000 men. One trial, the European Randomised Study of Screening for Prostate Cancer (n = 182,160), demonstrated a reduction in prostate cancer-related mortality at 9-years follow-up, but no reduction in total mortality. Since all-cause mortality was not reduced, policy makers rightly questioned the propriety of advising large-scale screening if the overall rate of death was not altered.

The European Randomized Study of Screening for Prostate Cancer now has data on up to 13 years of follow-up, which remain concordant with their findings at 9 and 11 years: a reduction in prostate cancer mortality (rate ratio 0.79, or a 21% reduction), but again no reduction in all-cause mortality.

Although a 21% relative reduction in prostate cancer mortality might seem impressive, the absolute risk reduction is much less so: avoidance of one prostate cancer death/781 men screened. Based on the recommendations of the United States Preventive Services Task Force, most primary care clinicians have minimized screening of average-risk adult men for prostate cancer. These results confirm the rationale for that clinical posture. ■

Doing the Right Thing for Acute Bronchitis in Healthy Adults: Antibiotics

SOURCE: Smith S. Antibiotics for acute bronchitis. *JAMA* 2014;312:2678-2679.

The scenario is commonplace, evokes sympathy, and might even make you feel a little uncomfortable: Your third patient of the morning comes in with an apparently viral bronchitis, with the chief complaint of "I need some antibiotics." While an antibiotic prescription might seem to be the path of least resistance, the literature does not provide support that it is the wisest path.

Most cases of acute bronchitis in healthy individuals are viral. A review of seven randomized trials found that antibiotic treatment provided a short-term benefit of .5 day shorter duration of cough than placebo. This modest benefit needs to be weighed in comparison to the many adverse effects associated with antibiotic administration. Concordant with these observations, the National Institute for Care Excellence (United Kingdom) guidelines have suggested that antibiotics not be used for healthy persons in the absence of pneumonia.

While some patients will be disappointed if antibiotics are not dispensed, an explanation of the risk:benefit ratio will often assuage them. Despite increasing awareness of the limited benefits of antibiotics, over-prescribing remains commonplace. ■

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CME QUESTIONS

1. The economic burden associated with diagnosed and undiagnosed diabetes in the United States costs each American approximately:

a. $1000 annually

b. $750 annually

c. $1250 annually

d. $4200 annually

2. A 58-year-old man was discharged 1 week ago following an acute anterior wall myocardial infarction. He is asymptomatic and remains in a stable marital relationship. His blood pressure is 130/80, lipids normal, and he is taking a beta-blocker and aspirin. He inquires as to when he may resume sexual activity with his wife. Which of the following statements is *true*?

a. A treadmill test is recommended prior to resuming sexual activity.

b. Patient is considered "low risk" and may resume sexual activity immediately.

c. Patient should be encouraged to wait 8 weeks prior to initiating sexual activity

d. Patient should take a nitroglycerin tablet 0.4 mg SL prior to attempting intercourse to reduce risk of acute myocardial infarction.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Statins and the Neuromuscular System

Revascularization for Isolated Proximal LAD