

**Response to Reviewers:**

Name of journal: *World Journal of Medical Genetics*

ESPS Manuscript NO: 8339

**Molecular genetics of gastric adenocarcinoma in clinical practice****Reviewer #1 (00505468)**

**Criticism #1:** This is a well-written review on an interesting topic. In fact patients undergoing vascular surgery are exposed to higher morbidity and mortality as compared to other surgical patients due to the coexistence of diffuse atherosclerotic disease. My suggestions are the following: 1 Hypertension control prior as well as during surgery is an important element of good outcome after surgery as well as for long-term survival.

**Response to criticism #1:** We agree with the reviewer on the importance of blood pressure control in the perioperative period and during long-term follow-up. We have added the following "Current guidelines recommend aggressive blood pressure control in patients with PAD, in particular in patients with diabetes and/or chronic kidney disease (goal < 130/80 mmHg) (1). In the HOPE (Heart Outcomes Prevention Evaluation) trial ramipril 10 mg was associated with a 22% reduction in cardiovascular events and is currently recommended for high-risk patients, including those with PAD (2)."

**References:**

1- ESH/ESC. 2003 European Society of Hypertension-European Society

of Cardiology guidelines for the management of arterial hypertension.

J Hypertens 2003;21(6):1011-53.

2- Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342(3):145-53.

**Criticism #2:** The beneficial effects of statins prior to vascular surgery as well as after has been shown in several publications. Therefore for the completeness of this very important Review Paper I would suggest the authors to expand their work in order to include the above-mentioned issues.

**Response to criticism #2:** We agree with this comment. In fact we have previously shown that treatment with statins was an independent predictor of long-term survival after vascular surgery (1). We have added the following to the manuscript: "Statins may play a pivotal role in plaque stabilization by reducing circulating levels of inflammatory cytokines, increase expression of nitric oxide synthase, and reduced production of endothelin-1 and reactive oxygen species. Additionally, there is evidence from randomized clinical trials and observational studies to support its use in clinical practice. In the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE-III) study high-dose fluvastatin reduced the composite of cardiovascular death and non-fatal myocardial infarction by 53% among 457 patients undergoing vascular surgery (2). In a smaller trial involving 100 vascular patients randomly assigned to 20 mg of atorvastatin or placebo, statins reduced cardiac events from 26% to 8%

at 6 months (3). An observational study of 164 veterans undergoing vascular surgery at our institution demonstrated that statin use was associated with a significant reduction in long-term mortality (1). Current guidelines recommend the use of statins in patients with peripheral arterial disease to reduce cardiovascular events (4).”

#### References:

1. Marston N, Brenes J, Garcia S, et al. Peak postoperative troponin levels outperform preoperative cardiac risk indices as predictors of long-term mortality after vascular surgery Troponins and postoperative outcomes. *J Crit Care*. Feb 2012;27(1):66-72.
2. Schouten O, Boersma E, Hoeks S.E, et al for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group (DECREASE). Fluvastatin and Perioperative Events in Patients Undergoing Vascular Surgery. *NEJM* 2009; 361: 980-9
3. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg*. May 2004; 39(5):967-975; discussion 975-966
4. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. Jan 2007;45 Suppl S:S5-67.

#### **Reviewer #2 (00391146):**

**Criticism #1:** Interesting well-written review paper. The comparison with the previous studies is correct. However, I have only one criticism. A short separate paragraph about current problems should be summarized at the end of the text

**Response to criticism #1:** A short paragraph titled “Summary of Current Problems” was added as follows:

**Summary of Current Problems:**

“Patients with PAD in need of elective vascular surgery have a high prevalence of coronary atherosclerosis and are at increased risk of perioperative myocardial infarction. Coronary revascularization prior to the vascular operation is not an effective intervention to mitigate this risk. A strategy of widespread use of cardiac troponins in the perioperative period is recommended to detect perioperative ischemic events associated with a long-term mortality risk. The selective use of medical interventions, cardiac imaging and coronary angiography in this population deserves further study.”

**Reviewer #3 (00276417)**

**Criticism #1:** I would like to congratulate the authors for an excellent manuscript on an important topic. However there is one question to be answered and two minor corrections to be made. These are: Comments In page 1, paragraph 2, line 2: It states: Peripheral arterial disease and coronary artery disease (CAD) often times coexist It should have stated: Peripheral arterial disease and coronary artery disease (CAD) often coexist

**Response to criticism #1:** Agree with the reviewer. We have corrected this sentence as recommended by the reviewer as follows: “Peripheral arterial

disease and coronary artery disease (CAD) often coexist in the same patient and..."

**Criticism #2:** In page 4, paragraph 1, line 2: it states: acuity of the condition that often times hampers the ability to start preoperative It should have stated: acuity of the condition that often hampers the ability to start preoperative..

**Response to criticism #2:** Agree with the reviewer. We have corrected this sentence as recommended by the reviewer as follows: " ... and the acuity of the condition that often hampers the ability to start preoperative interventions to mitigate cardiac risk."

**Criticism #3:** In page 9, second paragraph, last sentence states: This is best achieved with judicious utilization of beta-blockers, analgesia, and fluid administration with the intention to preserve double product. Do the authors mean in the last phrase to say (to preserve cardiac output)?? If not, then what do they mean by the double product?

**Response to criticism #3:** Double product refers to heart rate x systolic blood pressure, both of which are important determinants of myocardial oxygen consumption (MVO<sub>2</sub>). It is thought that ischemic events in the perioperative period are caused by an imbalance between oxygen supply and demand (type II MIs) in the setting of underlying severe coronary artery disease that is unmasked by the stress of the surgery. For example, in the POISE trial for every 10-

beats/min increase in heart rate there was a 31% relative increase in the odds of perioperative MI.

We have modified the text as follows: “This is best achieved with judicious utilization of beta-blockers, analgesia, and fluid administration with the intention to avoid tachycardia and hypotension.”