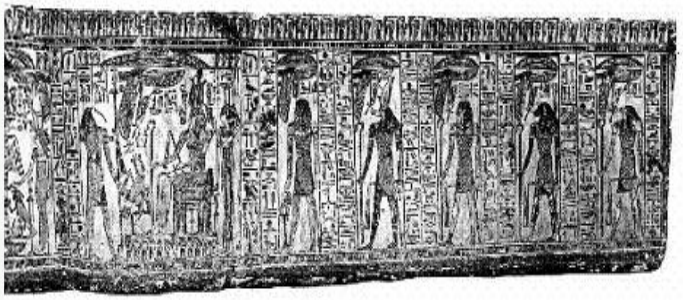
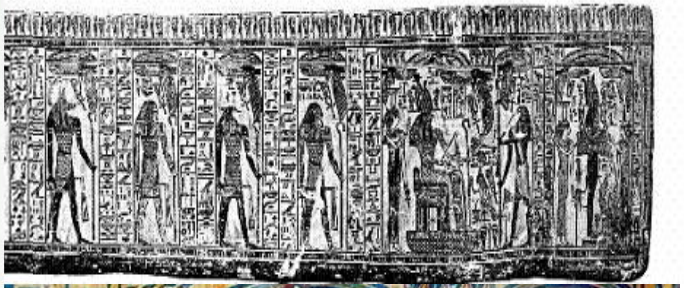
The Obesity Paradox in Surgical Patients: From Preoperative Assessment to Long-Term Outcome





Wael Galal Mohamed Mostafa

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Cover : Wael Galal Mohamed Mostafa

Cover content : The lady “Tayuheret” from the intermediate ancient Egyptian period, the 21st Dynasty, Circa 1069-945 B.C., lived as obese woman, approximate height 161 cm, died in her fifties, wrapped in her coffin (middle) , parts of her cabinet (right images and top left), grave (lower left). The sculptures of her tomb show her past and presumed future lifes.

The author wrote his name in English and hieroglyphic as ancient Egyptians would make (left side)

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The obesity paradox in surgical patients: from preoperative assessment to long term outcome

De obesitas paradox bij chirurgische patiënten: van preoperatief onderzoek tot uitkomsten op de lange termijn

Thesis

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Prof.dr. H.A.P. Pols

and in accordance with the decision of the Doctorate Board

The public defence shall be held on

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By

Wael Galal Mohamed Mostafa
born in Tanta, Egypt

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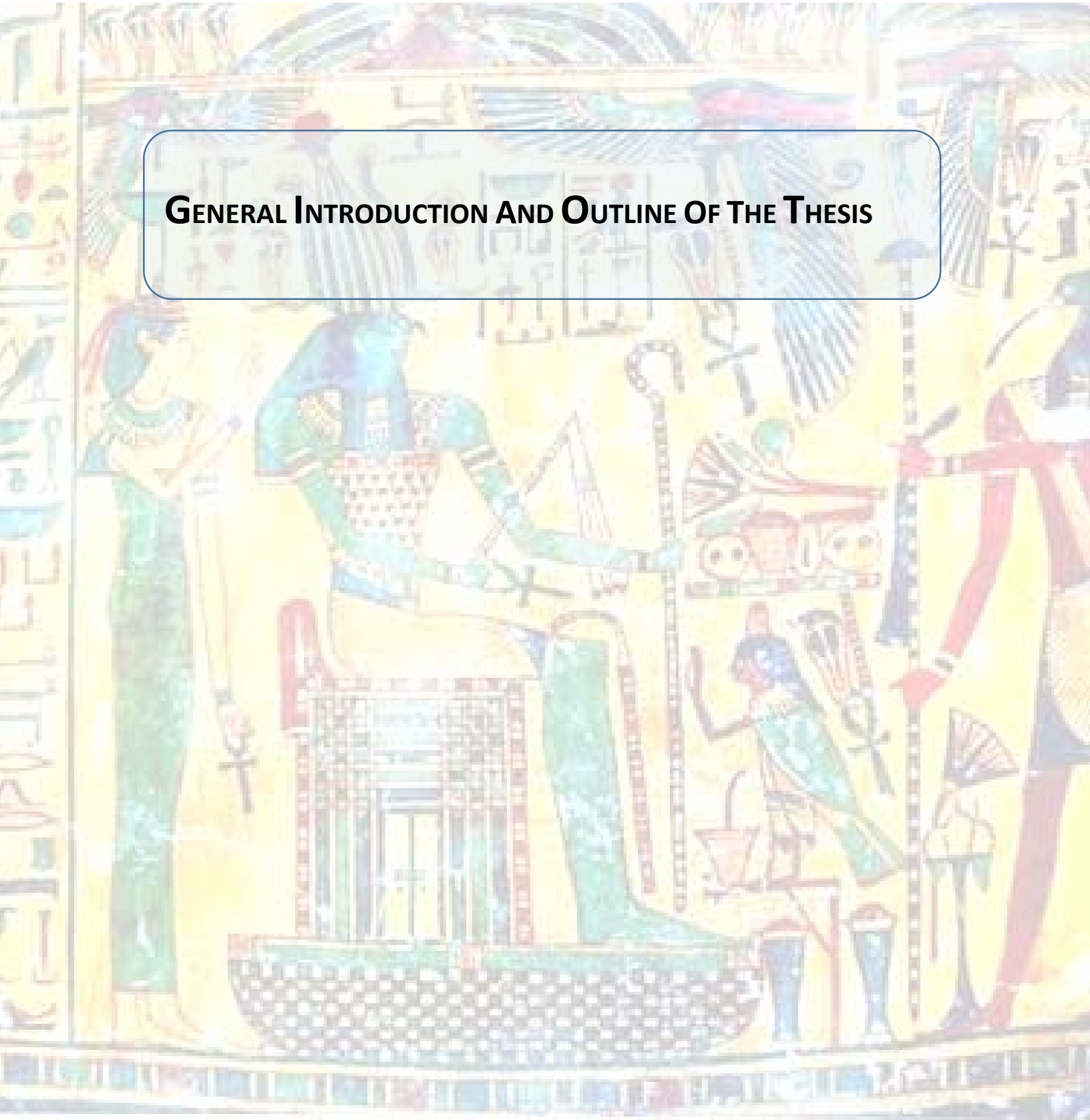


General Introduction and Outline of the Thesis

Introduction

In the Netherlands, 16 million inhabitants undergo about 1 million surgical procedures annually. The percentage of serious adverse advents is a burden to society and stresses the need for adequate preoperative assessment in order to select and optimize surgical patients. The clinical course of surgical patients have been the subject of research focusing on perioperative outcome. [1-6] The influenced time frame expanded from merely improving the direct postoperative surgical outcome to influencing the long term outcome of the surgical patient. [7-14] Consequently, advances in perioperative care emphasize a more important role of the preoperative evaluation and a more comprehensive risk stratification by the anesthesiologist. Recognition and optimization of chronic disease processes prior to surgery could prove beneficial by reducing the risk of complications, not only in the perioperative stage, but also on longer-term follow up. With the growing number of surgical procedures performed yearly in modern societies we believe anesthesiologists have a golden opportunity to influence the health and quality of life of their patients not only during the perioperative phase, but also in order to lower the incidence of long-term adverse outcomes

Short and long-term adverse outcomes related to vascular surgery are mainly cardiovascular in nature. [15, 16] Perioperative myocardial infarction is the most frequent serious complication. These adverse events consequently lead to significant morbidity and mortality. [17] The pathophysiologic cascade leading to perioperative myocardial ischemia is in about 50% of cases due to acute plaque rupture in coronary arteries and in over 50% due to an oxygen supply and demand imbalance. [18, 19] Therefore, it seems very interesting for clinicians; particularly those involved in anesthetic and perioperative surgical care; to predict and prevent perioperative myocardial ischemia and infarction, and to implement evidence-based perioperative guidelines. [20, 21]

Our research mainly involved patients undergoing vascular surgery. Because of the expected adverse cardiac events in the vascular surgical patient, particular attention was directed towards cardiac ischemic testing and monitoring. Dobutamine echocardiography has been an established method to predict the need for preoperative revascularization prior to elective vascular surgery in high-risk vascular surgical patients according to the recommendations of both the European Society of Cardiology and the the European Society of Anesthesia (ESC/ESA) guidelines on non-cardiac surgery along with the American College of Cardiology Foundation and the American Heart Association (ACC/AHA). [20, 21] However, preoperative revascularization in vascular surgery patient has

not proven to be beneficial. [22] Because myocardial ischemia can occur during surgery as well, transesophageal echocardiography was used to cover the intraoperative phase. An important question is whether the site of intraoperative ischemic events might or might not correlate with the findings of preoperative stress echocardiographic testing.

Despite pre- and intra-operative optimization, the incidence of perioperative myocardial infarction in this population remains high. Clinical signs, ECG changes, echocardiographic new wall abnormalities and biochemical markers are required for the diagnosis of myocardial infarction but these findings are less useful occurring in the postoperative phase. Moreover, the occurrence of subclinical ischemic events is strongly related to adverse long-term cardiac outcomes. [23, 24] Up to now, it is unclear which therapeutic intervention would be appropriate in this situation.

Surgical procedures are more and more performed at higher age, so patients suffering from multiple chronic diseases are encountered more frequently than in the past. Since the second half of the 20th century, obesity has become a growing problem in many parts of the world. A Belgian scientist and mathematician; Adolphe Quetelet; first introduced the body mass (formerly known as Quetelet's index) index (BMI) to public health science in the 19th century as gross index of body fat content. This index was used as a nutritional estimate for a long-time until the epidemic of obesity raised much attention to obesity and its associated health risks. Definition of obesity was hence primarily based on determination of an individual's BMI by virtues of its simplicity before other more specific measures of total or particular body-fat content were introduced. The World Health Organisation and the National Institute of Health (NIH) distinguished 4 main quartiles of BMI. Especially the differences between a female pear shaped and a male apple shaped patterns were subject of discussion. The latter was considered as more harmful as it is more often related to fat in abdominal viscera and the mesentery, and associated with the metabolic syndrome; a combination of hypertension, (pre)diabetes, hyperlipidemia, and hypercholesterolemia.

Consequently, ageing, co-morbidity, and obesity became more common among vascular surgical patients. Aging and obesity are strongly associated with overt or occult cardiac disease. A preponderance of cardiovascular metabolic risk factors were found in the overweight and obese patients. [25, **26**] Not only these risk factors imply cardiac risk, but also obesity itself is known to be related to left-ventricular morphological changes and impaired function. [27] Increased body mass was found a predictor of increased cardiac risk independent of other cardiac risk factors as hypertension, diabetes and hypercholesterolemia. [**26**] These facts led to the presumption that patients with higher BMI have higher mortality rates than patients with lower weight. In fact, previous studies suggested

a strong link between obesity and mortality of cardiovascular origin that is independent of other cardiovascular risk factors. [28-30]

Just following the start of the new millennium, an article from another Erasmus MC research group announced the discovery of a new epidemiologic phenomenon: the body mass index paradox. [31] In the following years, many publications reported its occurrence in particular medical populations characterized by chronic debilitating illnesses. We investigated the obesity paradox in several different surgical populations.

Outline of this thesis

The aim of the first part of this thesis was to explore the possible existence of the obesity paradox in surgical patients particularly those with peripheral arterial disease, coronary artery disease, and COPD. Observation of such newly reported phenomenon mandated us to look for any possible influencing factor such as cachectic phenomena and cardiovascular risk factors.

Part I: The body mass index paradox

Chapter 1. In view of earlier reports of the obesity paradox in particular medical patient populations hallmarked by chronicity, and our particular interest in perioperative cardiovascular medicine, we studied patients undergoing peripheral arterial surgery. We conducted this retrospective study to validate the existence of such phenomenon in surgical patients with known or suspected coronary artery disease. The study examined the long-term relationship between the population's BMI divided into the four quartiles defined by the World Health Organization, and long-term mortality.

Chapter 2. The Erasmus University Medical Centre adopted an elaborative preoperative screening strategy to identify patients with chronic obstructive pulmonary diseases (COPD) by performing preoperative pulmonary function testing (PFT). This study was conducted in order to provide further explanation of the BMI-mortality paradox in a group of peripheral arterial disease patients who underwent pulmonary function testing preoperatively. We examined the association of BMI with the severity of COPD.

Chapter 3. Only few studies have reported about the obesity paradox in surgical patients. We analyzed a large population of 10,427 surgical patients who underwent a variety of surgical procedures. In this study we investigated the association between BMI categories and both short- and long-term mortality and length of hospital stay.

Chapter 4. Because the populations we examined represented mainly vascular surgical patients with peripheral arterial disease, we investigated another risk factor dictated directly by this group of patients, i.e. the association with polyvascular disease. In this retrospective study, the interaction of BMI categories with polyvascular disease and targets of treatment were examined.

Chapter 5. In order to summarize the knowledge from the current literature, we presented these data in a review article on the obesity paradox in surgical patients.

Part II: Expanding the Utility of Perioperative and Intraoperative Echocardiography

As major perioperative complications related to vascular surgery are cardiovascular in nature and echocardiography is the most used functional cardiovascular evaluation tool in today's practice, we investigated the use of perioperative echocardiography targeting the management of two of the most functionally impairing complications in non-cardiac surgery; i.e. myocardial ischemia/infarction and heart failure.

Chapter 6. Preoperative revascularization had not proven to decrease mortality in vascular surgery patients with evidence of coronary artery disease prior to non-cardiac surgery. We investigated whether the site of new wall motion abnormalities detected by dobutamine stress echography in 54 patients undergoing major vascular surgery corresponded with intraoperatively new wall motion abnormalities revealed by intraoperative transesophageal echocardiography. Postoperatively, myocardial ischemia and cardiac death were recorded and these patients were monitored biochemically and electrocardiographically to determine the occurrence of myocardial ischemia and/or infarction.

Chapter 7. This study was conducted to evaluate the prevalence of left ventricular dysfunction in vascular surgical patients prior to surgery and assess the adherence to the current European Society of Cardiology (ESA) recommendations to improve the left ventricular function in this population.

References

1. Jeger RV, Probst C, Arsenic R, Lippuner T, Pfisterer ME, Seeberger MD, Filipovic M. Long-term prognostic value of the preoperative 12-lead electrocardiogram before major noncardiac surgery in coronary artery disease. Am Heart J. 2006;151: 508-13

2. Lucreziotti S, Foroni C, Fiorentini C. Perioperative myocardial infarction in noncardiac surgery: the diagnostic and prognostic role of cardiac troponins. J Intern Med 2002;252:11-20

3. Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gürke L, Skarvan K, Seeberger MD. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. J Am Coll Cardiol. 2003;42:1767-76

4. Dunkelgrun M, Schreiner F, Schockman DB, Hoeks SE, Feringa HH, Goei D, Schouten O, Welten GM, Vidakovic R, Noordzij PG, Boersma E, Poldermans D. Usefulness of preoperative oral glucose tolerance testing for perioperative risk stratification in patients scheduled for elective vascular surgery. Am J Cardiol. 2008;101:526-9

5. Ryding AD, Kumar S, Worthington AM, Burgess D. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. Anesthesiology. 2009;111:311-9

6. Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G, Sharma SC, Vezeridis M, Khuri SF, Friedmann PD. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA. 2007;297:2481-8

7. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol. 2003;42:1547-54

8. Hoeks SE, op Reimer WJ, van Gestel YR, Smolderen KG, Verhagen H, van Domburg RT, van Urk H, Poldermans D. Preoperative cardiac risk index predicts long-term mortality and health status. Am J Med. 2009;122:559-65.

9. Feringa HH, Bax JJ, Hoeks S, van Waning VH, Elhendy A, Karagiannis S, Vidakovic R, Schouten O, Boersma E, Poldermans D. A prognostic risk index for long-term mortality in patients with peripheral arterial disease. Arch Intern Med. 2007;167:2482-9

10. Payne CJ, Gibson SC, Bryce G, Jardine AG, Berry C, Kingsmore DB. B-type natriuretic peptide predicts long-term survival after major non-cardiac surgery. Br J Anaesth 2011;107:144-9

11. Goei D, van Kuijk JP, Flu WJ, Hoeks SE, Chonchol M, Verhagen HJ, Bax JJ, Poldermans D. Usefulness of repeated N-terminal pro-B-type natriuretic peptide measurements as incremental predictor for long-term cardiovascular outcome after vascular surgery. Am J Cardiol. 2011;107:609-14.

12. Back MR, Leo F, Cuthbertson D, Johnson BL, Shamesmd ML, Bandyk DF. Long-term survival after vascular surgery: specific influence of cardiac factors and implications for preoperative evaluation. J Vasc Surg. 2004;40:752-60

13. Welten GM, Schouten O, Chonchol M, Hoeks SE, Feringa HH, Bax JJ, Dunkelgrün M, van Gestel YR, van Domburg RT, Poldermans D. Temporary worsening of renal function after aortic surgery is associated with higher long-term mortality. Am J Kidney Dis 2007; 50:219-28

14. Manku K, Bacchetti P, Leung JM. Prognostic significance of postoperative in-hospital complications in elderly patients. I. Long-term survival. Anesth Analg 2003;96:583-9

15. Mangano DT. Perioperative cardiac morbidity. Anesthesiology. 1990;72:153-84

16. Kertai MD, Klein J, van Urk H, Bax JJ, Poldermans D. Cardiac complications after elective major vascular surgery. Acta Anaesthesiol Scand 2003;47: 643-54

17. Sprung J, Abdelmalak B, Gottlieb A, et al. Analysis of risk factors for myocardial infarction and cardiac mortality after major vascular surgery. Anesthesiology 2000;93: 129-40

18. Dawood MM, Gupta DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57: 37-44

19. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005; 173:627-34

20. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C; Authors/Task Force Members. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014 Sep 14;35(35):2383-431

21. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN; American College of Cardiology; American Heart Association. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014 Dec 9;64(22):e77-137

22. McFalls EO1, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004 Dec 30;351(27):2795-804

23. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012 Jun 6;307(21):2295-304

24. van Waes JA, Nathoe HM, de Graaff JC, Kemperman H, de Borst GJ, Peelen LM, van Klei WA; Cardiac Health After Surgery (CHASE) Investigators. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation. 2013 Jun 11;127(23):2264-71

25. Gokulakrishnan K, Deepa M, Monickaraj F, Mohan V. Relationship of body fat with insulin resistance and cardiometabolic risk factors among normal glucose-tolerant subjects. J Postgrad Med 2011;57:184-8.

26. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, van Dam RM, Hu FB, Visscher TL, Menotti A, Thorpe RJ Jr, Jamrozik K, Calling S, Strand BH, Shipley MJ; for the BMI-CHD Collaboration Investigators. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med. 2007;167:1720-8

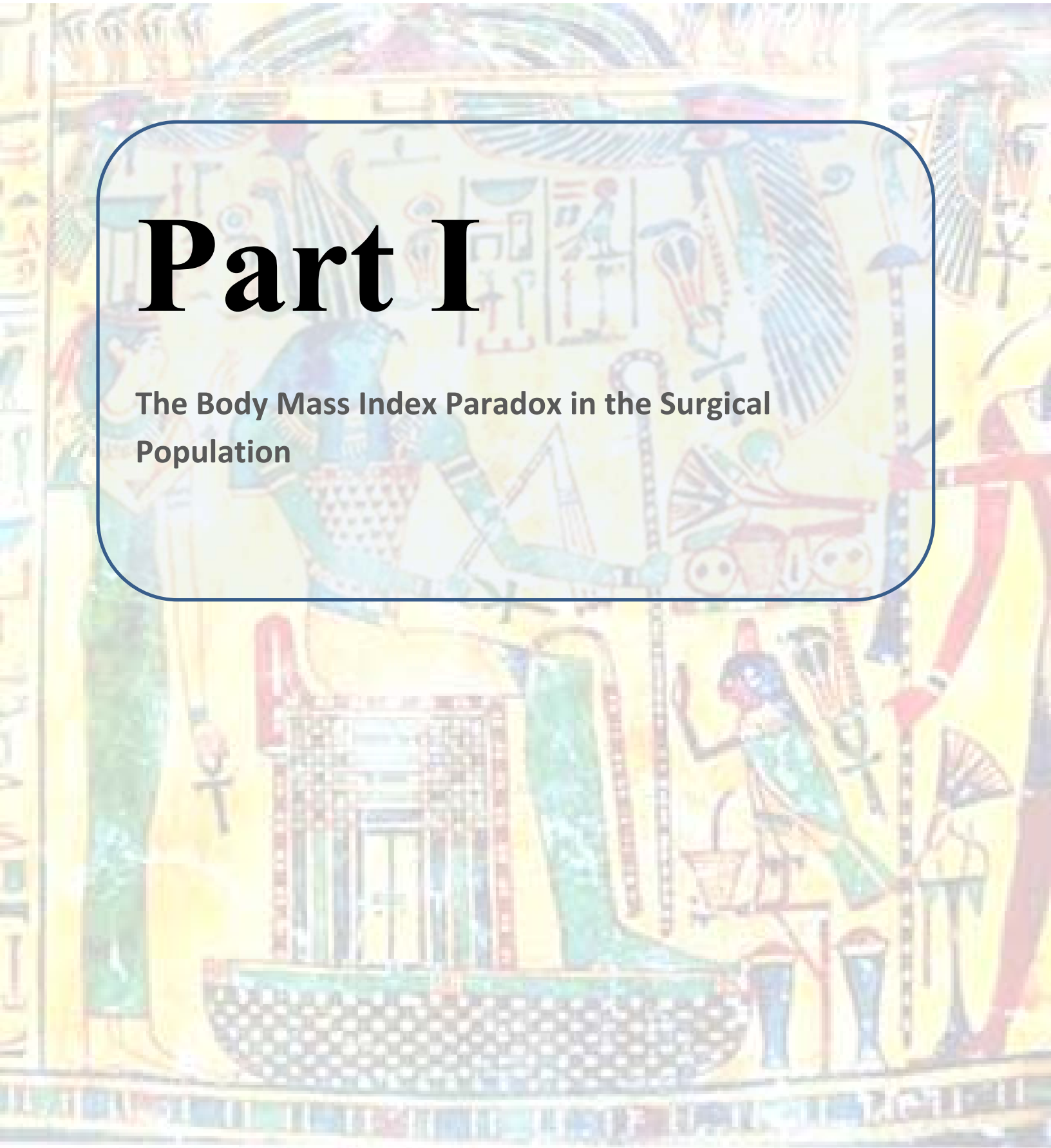
27. Lavie CJ, Milani RV, Ventura HO, et al. Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction. Am J Cardiol 2007;100:1460-4

28. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM. Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20,000 Dutch men and women aged 20-65 years. Eur J Cardiovasc Prev Rehabil. 2009;16:729-34

29. Faeh D, Braun J, Tarnutzer S, Bopp M. Obesity but not overweight is associated with increased mortality risk. Eur J Epidemiol 2011;26:647-55

30. Logue J, Murray HM, Welsh P, Shepherd J, Packard C, Macfarlane P, Cobbe S, Ford I, Sattar N. Obesity is associated with fatal coronary heart disease independently of traditional risk factors and deprivation. Heart 2011;97:564-8

31. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2001;38:789-95



Part I

The Body Mass Index Paradox in the Surgical Population

CHAPTER 1

Relation of Body Mass Index to Outcome in Patients with Known or Suspected Coronary Artery Disease

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Relation of Body Mass Index to Outcome in Patients with Known or Suspected Coronary Artery Disease

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Abstract

Increased body mass index (BMI), a parameter of total body fat content, is associated with an increased mortality in the general population. However, recent studies have shown a paradoxic relation between BMI and mortality in specific patient populations. This study investigated the association of BMI with long-term mortality in patients with known or suspected coronary artery disease. In a retrospective cohort study of 5,950 patients (mean age 61 ± 13 years; 67% men), BMI, cardiovascular risk markers (age, gender, hypertension, diabetes, current smoking, angina pectoris, old myocardial infarction, heart failure, hypercholesterolemia, and previous coronary revascularization), and outcome were noted. The patient population was categorized as underweight, normal, overweight, and obese based on BMI according to the World Health Organization classification. Mean follow-up time was 6 ± 2.6 years. Incidences of long-term mortality in underweight, normal, overweight, and obese were 39%, 35%, 24%, and 20%, respectively. In a multivariate analysis model, the hazard ratio (HR) for mortality in underweight patients was 2.4 (95% confidence interval [CI] 1.7 to 3.7). Overweight and obese patients had a significantly lower mortality than patients with a normal BMI (HR 0.65, 95% CI 0.6 to 0.7, for overweight; HR 0.61, 95% CI 0.5 to 0.7, for obese patients). In conclusion, BMI is inversely related to long-term mortality in patients with known or suspected coronary artery disease. A lower BMI was an independent predictor of long-term mortality, whereas an improved outcome was observed in overweight and obese patients.

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Key words: Body Mass Index; Coronary artery disease; Prognosis.

Condensed abstract

Clinical interest is currently focusing on the prognostic importance of body mass index in different patient categories rather than the general population. We retrospectively assessed the relation between body mass index (BMI) and long-term mortality in 5950 patients with known or suspected coronary artery disease. The mean follow-up time was 6 ± 2.6 years. BMI was inversely related to long-term mortality. A lower BMI was an independent predictor of long-term mortality, while in overweight and obese patients an improved outcome was observed.

Abbreviations

BMI:	Body mass index
CAD:	Coronary artery disease
HR:	Hazard ratio
95% CI:	95% confidence interval
MI:	Myocardial infarction
CABG:	Coronary artery bypass grafting
PCI:	Percutaneous coronary intervention

Introduction:

In this study, we evaluated the effect of body mass index (BMI) on long-term mortality of patients with known or suspected coronary artery disease (CAD) after controlling for coronary risk factors.

Patients and Methods

We retrospectively studied 5,950 adult patients with known or suspected CAD who were referred to the outpatient clinics of the Erasmus University Medical Center (Rotterdam, The Netherlands) between January 1993 and January 2005. Our study population consisted of high-risk patients referred to the vascular clinic for evaluation of systemic atherosclerosis, CAD or peripheral arterial disease, and for management of underlying risk factors. In these patients, BMI was measured at the time of the first visit and cardiac risk factors were noted. We categorized patients as having known (n = 2,486; 42%) or suspected (n = 3,464; 58%) CAD. Known CAD was indicated by the presence of angina pectoris, previous myocardial infarction (MI), or previous coronary revascularization (i.e., previous percutaneous coronary intervention and/or coronary artery bypass grafting). Patients with atypical chest pain, dyspnea, atypical electrocardiographic abnormalities (i.e., ST-segment changes without Q waves), or ≥2 cardiac risk factors (male gender, current smoker, hypertension, renal dysfunction, hypercholesterolemia, and diabetes) were considered to have suspected CAD.[1]

The hospital medical ethical committee approved the study protocol. Clinical data were obtained by thorough review of medical records and electronic databases and included age, height, weight, previous MI, angina pectoris, coronary artery revascularization, heart failure (HF), diabetes mellitus (fasting glucose level ≥7.0 mmol/L or requirement of hypoglycemic agents), hypertension (blood pressure ≥140/90 mm Hg or intake of antihypertensive medications), current smoker, hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L [213 mg/dl] or intake of lipid-lowering agents), and renal dysfunction (serum creatinine level ≥2.0 mg/dl [177 μmol/L] or requirement of dialysis). HF was considered if a patient had a history of shortness of breath on exertion or at rest, decreased physical ability, or swelling of lower limbs proved clinically or at echocardiography upon medical consultation to be valid for signs of cardiac decompensation.[2] Patients were assessed for cardiac medication use. BMI was calculated as body weight

(kilograms) divided by height squared (meters). Accordingly, patients were grouped according to BMI classifications of the World Health Organization[3] and the National Institutes of Health[4] as underweight (BMI <18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), or obese (≥30 kg/m^2).

End points were death from all causes and hard cardiac events (cardiac death or MI). Cardiac death was defined as death from any cardiac cause including sudden cardiac death, MI, congestive HF, cardiac arrhythmias, and death in which there is evidence of a primary cardiac cause that could not be classified as mentioned above. Sudden cardiac death was defined as unexpected natural death due to cardiac causes within 1 hour of onset of acute symptoms. Criteria of MI diagnosis included ≥2 of the following: high cardiac enzyme levels (creatine kinase [CK] level >190 U/L and CK-MB level >14 U/L, or CK-MB fraction >6% of total CK, or cardiac troponin T level >0.1 ng/ml), development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms at electrocardiography), and typical chest pain. Events were verified by review of hospital records or contacting general practitioners, civil registry, or participants' families (by questionnaires in telephone calls) if needed.

Statistical analysis was performed using the syntax commands of SPSS 13.0 for Windows (SPSS, Inc., Chicago, Illinois). Categorical variables are expressed as percentages and were compared using Pearson's chi-square test. Continuous variables are presented as mean ± SD and were compared using Student's *t* test. Primary end points were all-cause mortality and hard cardiac events (cardiac death and/or nonfatal MI). Cox proportional hazards models were used to determine univariate and multivariate predictors of mortality. Results on all-cause mortality, cardiac death, and MI were generated by Kaplan-Meier estimates and differences in mortality were compared using log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from a Cox proportional hazard stepwise regression model. Assumptions of the proportional hazard model (proportional hazard, lack of interaction, and linearity of continuous variables) were tested and found valid unless otherwise indicated. Proportional hazards assumptions were tested by constructing interaction terms between variables and time to each end point. Cox regression analyses showed no statistically significant interactions with time (each p value >0.05). Model selection is based on the stepwise principle, where the limits for entering and removing variables

were 0.05. BMI was divided into its quartiles in all statistical examinations. The group of normal weight patients served in analyses as the reference group (i.e., HR=1), and the risk of the other 3 BMI groups compared with this group was estimated by HRs from the proportional hazard models. Multivariate analysis was done by adjusting for all baseline characteristics including age, gender, and dobutamine stress echocardiographic results (to eliminate any significant interaction with other confounders). For all tests, a p value <0.05 (2-sided) was considered statistically significant.

Results

Distribution of BMI in the population was approximately normal, with a mean of 25.4 ± 4.0 kg/m^2 (Figure 1). Only 3% of the study population was underweight, 42% was normal or overweight, and 14% was obese. Clinical characteristics of the 4 BMI categories are presented in Table 1. Mean age was 60.8 ± 13 years and was not different across different BMI subsets. There were more men in the normal and overweight groups and more women in the underweight group. Current smokers were more prevalent in the underweight group. Diabetes and hypertension were noted more frequently in obese patients. Distribution of coronary risk factors across different groups is presented in Figure 2.

Patients were followed for a mean period of 6 ± 2.6 years. Minimum follow-up period was 6 months. In total, 3,828 of 5,950 patients (64%) were referred for dobutamine stress echocardiography after their initial visit. Stress-induced myocardial ischemia was assessed in 1,205 of 1,750 patients (69%) with known CAD and in 651 of 2,078 patients (31%) with suspected CAD. In total 1,786 of 5,950 patients underwent major vascular noncardiac surgery during the follow-up period. Of 1,786 patients, 38 (2.1%) died in the perioperative period. During follow-up, 1,697 patients (29%) died. Of these, 1,235 patients (21%) died from cardiac causes. Univariate associations between risk factors and long-term outcome are presented in Table 2. Underweight patients had a poor long-term outcome for all-cause and cardiac mortalities, whereas overweight and obese patients had more favorable long-term outcomes in terms of all-cause and cardiac deaths (Table 2). In a multivariable stepwise Cox regression model (Table 3), overweight and obese patients remained at significantly lower risk for all-cause mortality and cardiac mortality/MI. Underweight patients represented a high-risk category for all-cause mortality and cardiac death/MI.

Kaplan-Meier survival curves of the 4 BMI categories for an average interval of 6 ± 2.6 years are presented in Figure 3. Incidences of long-term mortality in underweight, normal, overweight, and obese patients were 39%, 35%, 24%, and 20%, respectively. In the same order, incidences of cardiac death/MI were 33%, 26%, 17%, and 14%. As shown in Figure 3, mortality hazard was inversely proportional to BMI ($p < 0.001$) for either type of mortality. Results were subsequently analyzed separately in patients with known CAD and in those with suspected CAD. An inverse relation between BMI and survival was observed in patients with suspected CAD (all-cause mortality, $p < 0.001$; cardiac death, $p < 0.001$) and in

patients with known CAD (all-cause mortality, p <0.001; cardiac death, p <0.001; Figure 4). In patients with suspected CAD, the underweight group had 2 short temporary shifts of improved survival over the normal weight group (4.5 to 5.5 and 6.5 to 8.5 years of follow-up), but eventually followed the same inverse relation with BMI at the commencement of follow-up. Overweight and obese populations showed the same paradoxic trend with BMI over the normal weight and underweight populations.

Discussion

The main finding of this study is that an inverse relation exists between BMI and incident all-cause and cardiac mortalities during long-term follow-up of patients with known or suspected CAD. Underweight patients had a greater than twofold increased risk of mortality compared with normal weight patients, with 40% less mortality and 20% less cardiac death in the obesity group. This reversed trend persisted after adjustment for coronary risk factors and was observed in patients with known CAD and those with suspected CAD.

Our population represented a cohort of ambulatory patients with normal distribution of risk factors and clinical suspicion and/or presentation of CAD. This population was composed of a broader spectrum of patients in contrast to previous studies conducted in isolated groups or after acute event or specific interventions. Previous studies have pointed out the prognostic influence of BMI in moribund patients with very limited functional capacity and/or short expectancy.[5-9] The effect of obesity on long-term outcomes in moribund patients with preserved functional capacity is an important issue. Our findings also show the contribution of coronary risk factors and other co-morbidities to the hazard of death in populations with different weights. In this regard, old MI remained a significant predictor of all-cause mortality (HR=1.5, 95% CI=1.3 to 1.7) and for cardiac death (HR=2.0, 95% CI=1.7 to 2.3) after correction for all other confounders.

In this population, crude death rate was 29% during a mean follow-up of 6 ± 3 years. Cardiac deaths were responsible for 73% of all deaths. Major risk factors (renal disease, diabetes, male gender, and smoking) were associated with increased long-term all-cause and cardiac mortality. As expected, co-morbid conditions (e.g., diabetes and hypertension) were more prominent in the obese population, whereas smoking and renal dysfunction were more prevalent in the underweight population.

As shown by Kaplan-Meier survival curves (Figure 4) patients with suspected CAD and those with proved CAD had similar long-term outcomes. The reason for this similar outcome might be related to the high incidence of asymptomatic CAD in patients with proved vascular disease.[10]

The paradoxic relation, a “protective effect”, of obesity on survival had been observed recently in several patient populations, such as patients with chronic HF or renal disease.[5,9,11] Curtis et al[11] examined a cohort of 7,767 outpatients with an established history of HF controlled under digitalis treatment. Higher BMIs were associated with a lower mortality.[11] These data confirmed previous survival data of 4,700 hospitalized patients with congestive HF associating an increased BMI with lower mortality ($p < 0.0001$).[9] Recently, Gruberg et al[12] studied patients who underwent percutaneous coronary intervention or coronary artery bypass grafting. The long-term mortality risk was similar across all BMI categories irrespective of type of revascularization procedure. Thus, overweight or obesity had no effect on crude survival at 3 years.[12] Sierra-Johnson et al[13] followed 389 patients undergoing cardiac rehabilitation and found an inverse relation between BMI and total and cardiovascular mortalities, although only the relation with cardiovascular mortality was statistically significant after adjustment for age and gender. Kragelund[14] examined the effect of BMI on survival in 6,676 consecutive patients with acute MI during 10-year follow-up. Overall obesity was inversely related to mortality from all causes. There was no association between obesity assessed as BMI and mortality (men, adjusted relative risk 0.90, 95% confidence interval 0.85 to 1.14, $p = 0.3$; women, adjusted relative risk 0.90, 95% confidence interval 0.74 to 1.10, $p = 0.2$).[14] Similar results were reported by Kennedy et al[15] who had examined BMI for all-cause mortality and cardiac death in 5,388 patients with complicated acute MI. Comparable results were assessed in patients with renal disease.[5,16] When a large cohort of patients with renal failure requiring dialysis ($n = 418,021$) was examined for survival, overweight and obese patients using dialysis had longer survival than did those with lower BMI.[7]

The reason for the paradoxic relation of BMI with mortality in the aforementioned patient populations is not understood. Although this pathomodulatory phenomenon is quite obscure, several influences can be suggested in our study. It had been previously demonstrated that peripheral adiposity (i.e., gynoid obesity) poses cardiovascular benefits due to secretion of adiponectin, which has anti-inflammatory, insulin-sensitizing, and antiatherogenic effects in addition to an association with lower total body fat content and the fact that subcutaneous body fat is relatively “inert” in metabolic and

inflammatory/mediation terms.[17] Abdominal obesity is associated with higher total body fat content, more insulin-resistance, more other co-morbid associations, and more metabolic activity and inflammatory cascading influences. Thus, an obesity paradox might be reflected from a higher prevalence of 1 obesity type (i.e., peripheral) over another (i.e., central), with its decelerating influences becoming more manifest as BMI increases to reach higher levels (i.e., >30 kg/m^2). It had been suggested that hypercholesterolemia and high levels of serum low-density lipoproteins associated with obesity serve a scavenging action against unbound circulating lipopolysaccharides with consequent anti-inflammatory response and improved long-term outcomes.[18] In the other extreme, it can be inferred from our population characteristics that active smokers were mostly in the normal BMI and underweight groups, an unsurprising finding knowing that those were the 2 groups with lowest survival. Loss of weight in geriatric patients, which might be related to malnutrition, multiorgan dysfunction, or unidentified occult malignancies (especially in the smoking population), had been identified as a significant predictor of mortality.[19,20] In this instance, those patients who presented at the time of evaluation with a BMI <18.5 kg/m^2 at ≥60 years of age represented a subcohort of patients at a higher risk of mortality. Most offending coronary risk factors were associated with a BMI >25 kg/m^2. Those patients with symptomatic co-morbidities were expected to have had consulted medical care, with a high probability that they were maintained on drugs proved to improve survival in a CAD population such as β blockers, statins, α_2 agonists and angiotensin-converting enzyme inhibitors.

One limitation of the study is its retrospective design. Due to time limits, we could not extend our follow-up beyond the date of conclusion. Data regarding waist circumference and waist/hip ratio that measures abdominal obesity were not routinely available. A more precise differentiation between peripheral adiposity and central compartment adiposity would have served to support the suggested hypothetical explanation about the role of a high BMI in prolonging survival in our patient population. Regarding the detection of our end points, a number of nonfatal asymptomatic MIs might have not been reported, especially if these occurred outside the hospital. Unfortunately, we have no data regarding a particular cause of cardiac death.

References:

1. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative repro¬ducibility and validity of systems for assessing cardiovascular func¬tional class: advantages of a new specific activity scale. Circulation 1981;64:1227-1234.

2. Remme WJ, Swedberg K. European Society of Cardiology Compre¬hensive guidelines for the diagnosis and treatment of chronic heart failure. Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Eur J Heart Fail 2002;4:11-22.

3. Energy and protein requirements: report of a joint FAO/WHO/UNU Expert Consultation. World Health Organ Tech Rep Ser 1985;724:1-206.

4. National Institutes of Health. Evidence-Based Guidelines: Clinical Guidelines on the Identification, Evaluation, and Treatment of Over¬weight and Obesity in Adults: Executive Summary. Bethesda, MD: National Heart, Lung, and Blood Institute, 2002.

5. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Hor- wich TB. Survival advantages of obesity in dialysis patients. Am J Clin Nutr 2005;81:543-554.

6. Davos CH, Doehner W, Rauchhaus M, Cicoira M, Francis DP, Coats AJ, Clark AL, Anker SD. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. J Card Fail 2003;9:29-35.

7. Snyder JJ, Foley RN, Gilbertson DT, Vonesh EF, Collins AJ. Body size and outcomes on peritoneal dialysis in the United States. Kidney Int 2003;64:1838-1844.

8. Halabi S, Small EJ, Vogelzang NJ. Elevated body mass index predicts for longer overall survival duration in men with metastatic hormone- refractory prostate cancer. J Clin Oncol 2005;23:2434-2435.

9. Gustafsson F, Kragelund CB, Torp-Pedersen C, Seibaek M, Burchardt H, Akkan D, Thune JJ, Kober L for the DIAMOND Study Group. Effect of obesity and being overweight on long-term mortality in congestive heart failure: influence of left ventricular systolic function. Eur Heart J 2005;26:58 -64.

10. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WFIII, Graor RA, Dewolfe VG, Maljovec LC. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and re¬sults of surgical management. Ann Surg 1984;199:223-233.

11. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, Kosiborod M, Portnay EL, Sokol SI, Bader F, Krumholz HM. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med 2005;165:55-61.

12. Gruberg L, Mercado N, Milo S, Boersma E, Disco C, van Es GA, Lemos PA, Ben Tzvi M, Wijns W, Unger F, Beyar R, Serruys PW, for the Arterial Revascularization Therapies Study Investigators. Arterial Revascularization Therapies Study Investigators. Impact of body mass index on the outcome of patients with multivessel disease

randomized to either coronary artery bypass grafting or stenting in the ARTS trial: the obesity paradox II? Am J Cardiol 2005;95:439-444.

13. Sierra-Johnson J, Wright SR, Lopez-Jimenez F, Allison TG. Relation of body mass index to fatal and nonfatal cardiovascular events after cardiac rehabilitation. Am J Cardiol 2005;96:211-214.

14. Kragelund C, Hassager C, Hildebrandt P, Torp-Pedersen C, Kober L. Impact of obesity on long-term prognosis following acute myocardial infarction. Int J Cardiol 2005;98:123-131.

15. Kennedy LM, Dickstein K, Anker SD, Kristianson K, Willenheimer R. OPTIMAAL Study Group. The prognostic importance of body mass index after complicated myocardial infarction. J Am Coll Cardiol 2005;45:156-158.

16. Kalantar-Zadeh K. Causes and consequences of the reverse epidemiology of body mass index in dialysis patients. J Ren Nutr 2005;15:142-147.

17. McCarty MF. A paradox resolved: the postprandial model of insulin resistance explains why gynoid adiposity appears to be protective. Med.Hypotheses 2003;61:173-176.

18. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, Coats AJ, Anker SD. The relationship between cholesterol and sur¬vival in patients with chronic heart failure. J Am Coll Cardiol 2003; 42:1933-1940.

19. Knudtson MD, Klein BE, Klein R, Shankar A. Associations with weight loss and subsequent mortality risk. Ann Epidemiol 2005;15:483-491.

20. Su D. Body mass index and old-age survival: a comparative study between the Union Army Records and the NHANES-I Epidemiolog¬ical Follow-Up Sample. Am J Hum Biol. 2005;17:341-354.

Figures

Figure 1: Distribution of study population according to their BMI values.

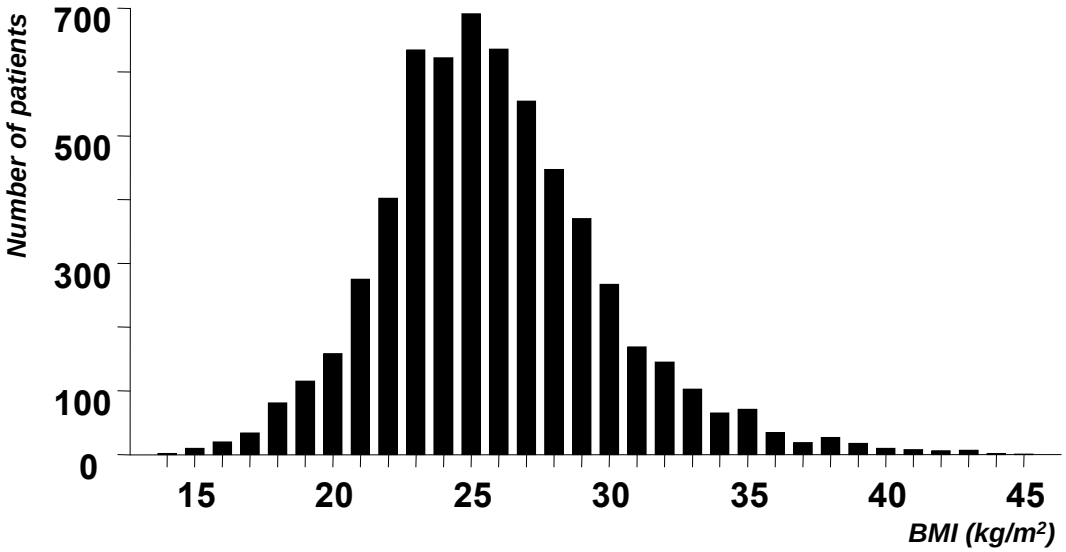


Figure 2: Categorical distribution of clinical characteristics and identified cardiac risk factors according to BMI indicating underweight (black bars), normal weight (dotted bars), overweight (white bars), or obesity (bars with horizontal stripes).

CABG (coronary artery bypass grafting); COPD (chronic obstructive pulmonary disease); DM (diabetes mellitus); PCI (percutaneous coronary intervention).

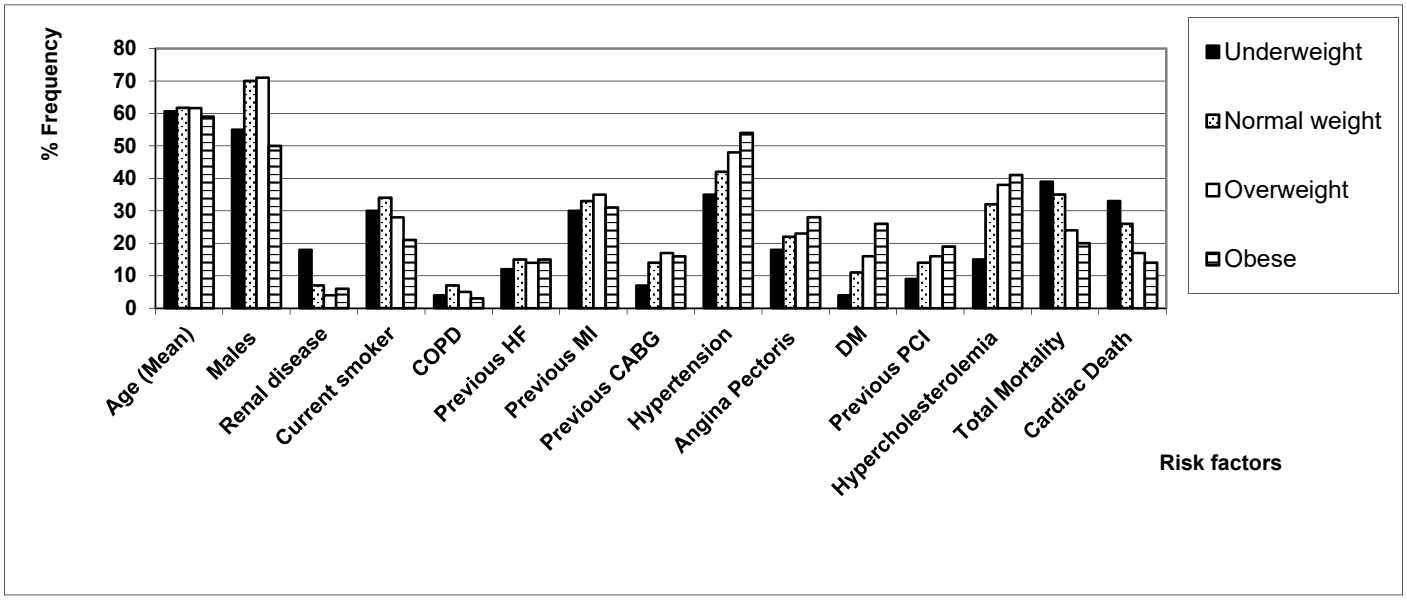
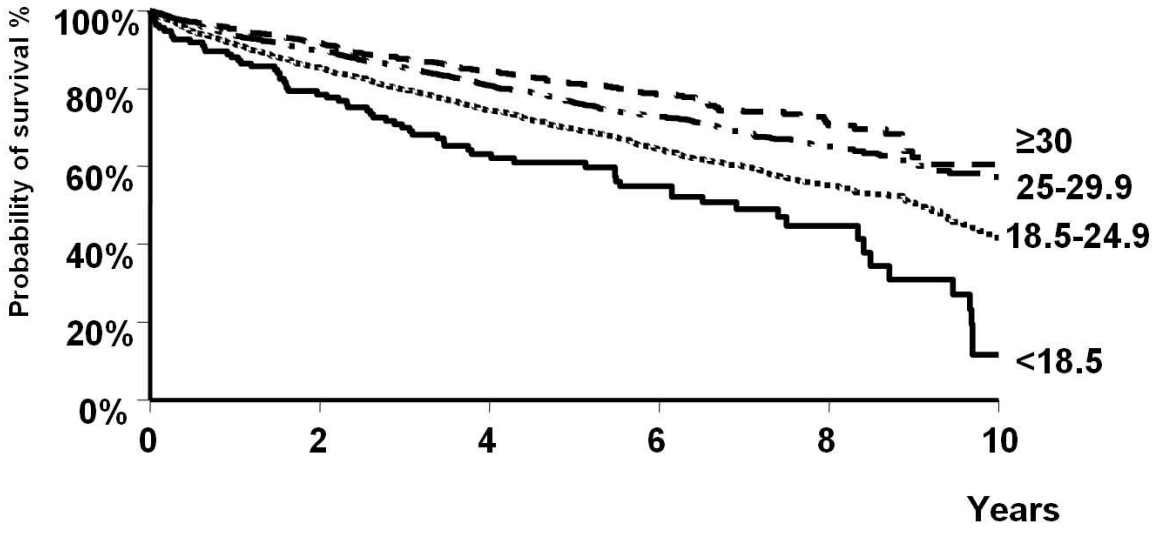


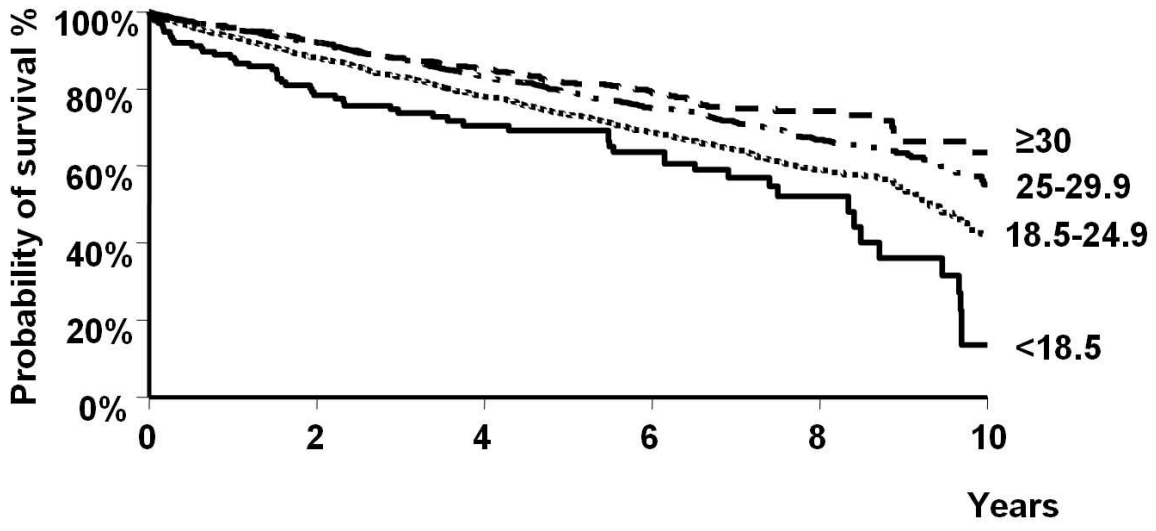
Figure 3. Kaplan-Meier survival curves of studied population showing mortality rate according to their BMI, in terms of;

(A) Total (all-cause mortality):



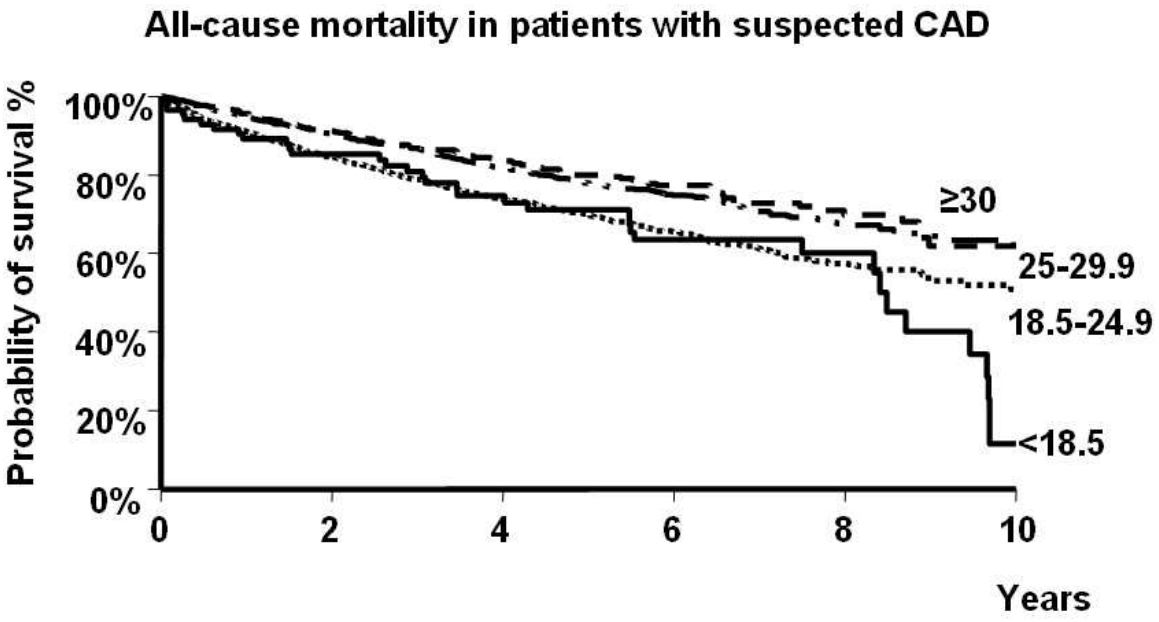
P<0.001

(B) Cardiac death:

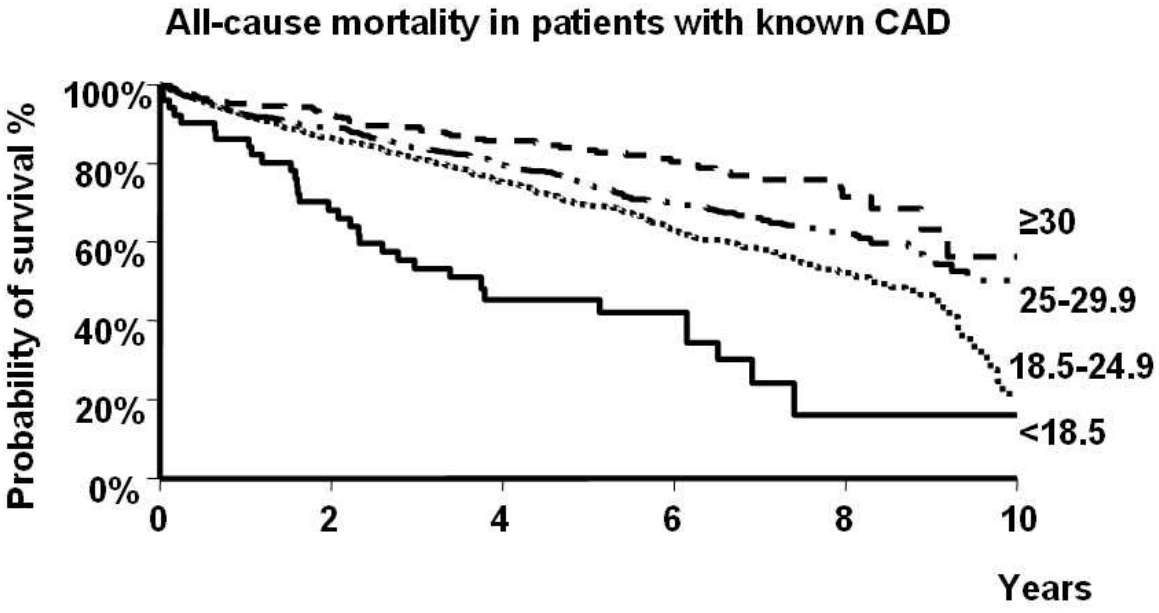


P<0.001

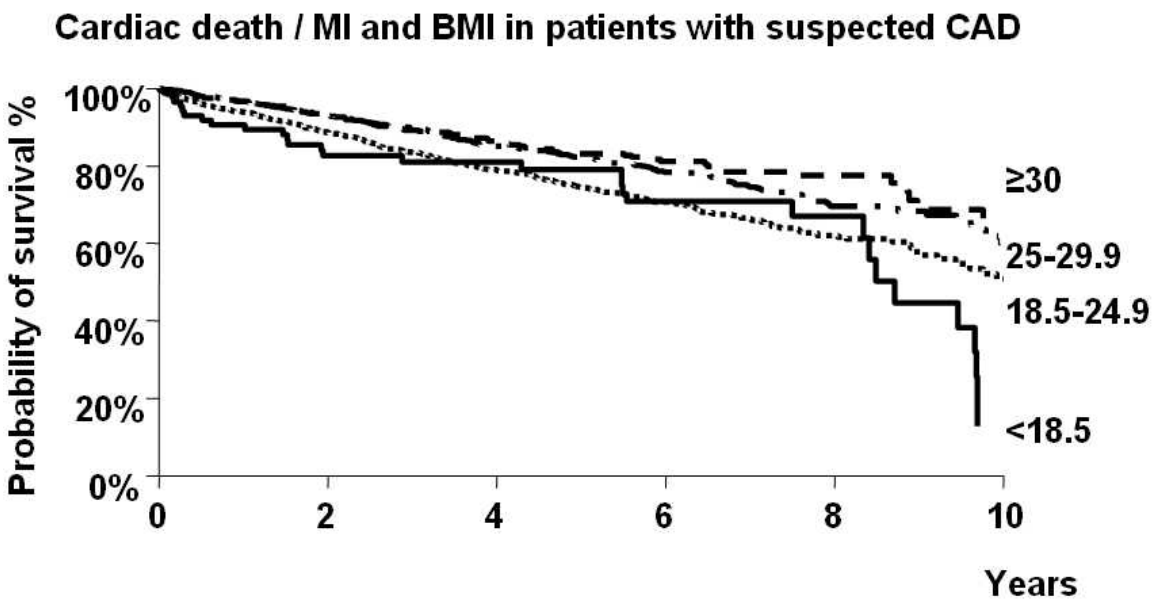
Figure 4. Examination of patients with known versus suspected CAD for total death *(upper figures)* and cardiac mortality/MI *(lower figures)*.



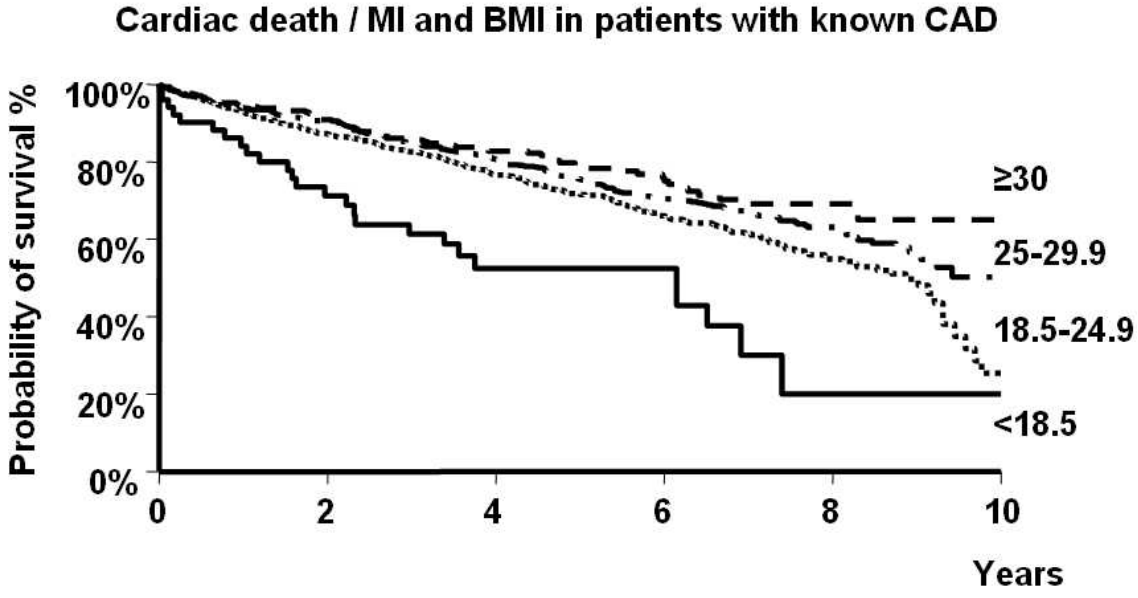
P<0.001



P<0.001


Cardiac death / MI and BMI in patients with suspected CAD
Probability of survival %
100%
80%
60%
40%
20%
0%
0
2
4
6
8
10
Years
≥30
25-29.9
18.5-24.9
<18.5

P<0.001


Cardiac death / MI and BMI in patients with known CAD
Probability of survival %
100%
80%
60%
40%
20%
0%
0
2
4
6
8
10
Years
≥30
25-29.9
18.5-24.9
<18.5

P<0.001

Tables

Table 1. Clinical characteristics of 5,950 patients according to body mass index

Variable	No. of Patients (%)	BMI (kg/m^2)				p Value
		<18.5 (n = 178, 3%)	18.5-24.9 (n = 2,499, 42%)	25-29.9 (n = 2,439, 41%)	>30 (n = 834, 14%)	
Age, mean ± SD	60.8 ± 12.6	60.7 ± 14.8	61.7 ± 13.3	61.7 ± 11.2	59.0 ± 11.3	0.7
Men	4,001 (67%)	98 (55%)	1,752(70%)	1,730(71%)	421 (50%)	<0.01
Current smoker	1,741 (29%)	53 (30%)	839 (34%)	673 (28%)	176(21%)	<0.01
Hypertension	2,737 (46%)	61 (35%)	1,050(42%)	1,173 (48%)	453 (54%)	<0.01
Angina pectoris	1,369 (23%)	32(18%)	545 (22%)	560 (23%)	232 (28%)	<0.01
Previous MI	1,964(33%)	53 (30%)	819 (33%)	841 (35%)	251 (31%)	0.13
Renal disease	363 (6%)	32(18%)	172 (7%)	108 (4%)	51 (6%)	<0.01
Chronic obstructive pulmonary disease	313 (5%)	6 (4%)	163 (7%)	116(5%)	27 (3%)	<0.01
History of HF	846 (14%)	20 (12%)	372 (15%)	332 (14%)	123 (15%)	0.51
Diabetes mellitus	883 (15%)	6 (4%)	267 (11%)	393 (16%)	217 (26%)	<0.01
Hypercholesterolemia	2,093 (35%)	27 (15%)	800 (32%)	924 (38%)	342(41%)	<0.01
Previous coronary by pass	929 (16%)	12 (7%)	359 (14%)	421 (17%)	137 (16%)	<0.01
Previous percutaneous coronary intervention	933 (16%)	16 (9%)	361 (14%)	394 (16%)	162 (19%)	<0.01
Known CAD	2,486 (42%)	51 (36%)	1,023 (41%)	1,085 (44%)	327 (39%)	0.01
Suspected CAD	3,464 (58%)	92 (64%)	149 (59%)	1,374(56%)	507 (61%)	0.01
Dobutamine stress echocardiography						
Wall motion abnormalities at rest	2,296 (38%)	98 (55%)	1,014(41%)	949 (39%)	235 (25%)	<0.01
New wall motion abnormalities	1,857 (31%)	68 (38%)	827 (33%)	787 (32%)	175 (21%)	<0.01

Table 2. Univariate association of clinical data with all-cause mortality and cardiac death/acute myocardial infarction mortality in univariate regression analysis

Variable	Total Mortality			Cardiac Death/Acute MI		
	No. of Patients	HR	95% CI	No. of Patients	HR	95% CI
Age		1.05	1.05-1.07		1.03	1.02-1.04
Men	1,333	2.1	1.8-2.4	1,234	2.0	1.8-2.3
Current smoker	600	1.7	1.5-1.9	557	1.6	1.4-1.8
Hypertension	848	1.3	1.1-1.4	816	1.4	1.2-1.5
Angina pectoris	335	0.8	0.7-0.9	338	0.9	0.8-1.0
Previous MI	659	1.4	1.3-1.6	686	1.9	1.7-2.2
Diabetes mellitus	301	1.4	1.2-1.6	275	1.3	1.1-1.6
History of HF	356	2.1	1.8-2.5	312	1.8	1.6-2.2
Hypercholesterolemia	451	0.6	0.6-0.7	535	1.2	0.8-1.5
Treated with statins	92	0.8	0.6-1.0	141	1.8	1.4-2.2
Untreated	359	0.6	0.5-0.7	394	0.8	0.7-1.0
Chronic obstructive pulmonary disease	166	3.1	2.5-4.0	156	3.0	2.4-3.8
Renal disease	73	4.5	2.9-7.0	74	2.9	2.0-4.4
Coronary bypass surgery	254	1.1	0.9-1.3	252	1.3	1.1-1.6
<5 yrs	66	0.5	0.4-0.7	62	0.7	0.4-0.8
Percutaneous coronary intervention	134	0.4	0.3-0.5	174	0.7	0.6-0.9
< 5 yrs	72	0.6	0.4-1.0	92	0.8	0.5-1.4
Dobutamine stress echocardiography						
Wall motion abnormalities at rest	724	1.30	1.16-1.46	704	1.36	1.21-1.53
New wall motion abnormalities	608	1.37	1.21-1.54	604	1.50	1.33-1.69
BMI groups						
Underweight	69	1.69	1.21-2.38	58	1.53	1.08-2.16
Overweight	596	0.63	0.55-0.71	422	0.75	0.66-0.85
Obese	163	0.47	0.39-0.57	117	0.58	0.48-0.69

Table 3. Multivariable regression analysis of total (all-cause) mortality and cardiac death/acute myocardial infarction mortality hazard adjusted for all patient variables

Variable	Total Mortality			Cardiac Death/Acute MI		
	No. of Patients	HR	95% CI	No. of Patients	HR	95% CI
Age		1.04	1.04-1.05		1.02	1.02-1.03
Men	1,333	1.9	1.7-2.2	1,234	1.7	1.5-2.0
Current smoker	600	1.6	1.4-1.9	557	1.5	1.3-1.7
Hypertension	848	1.3	1.2-1.5	816	1.4	1.2-1.6
Previous MI	659	1.5	1.3-1.7	686	2.0	1.7-2.3
Diabetes mellitus	301	1.5	1.3-1.8	275	1.4	1.2-1.7
History of HF	356	2.0	1.7-2.4	312	1.6	1.4-2.0
Hypercholesterolemia	451	0.8	0.7-0.9	535	1.2	1.0-1.4
Using statins	92	0.9	0.7-1.2	141	1.8	1.5-2.2
Untreated	359	0.8	0.7-0.9	394	1.0	0.8-1.2
Chronic obstructive pulmonary disease	166	2.4	1.8-3.2	156	2.3	1.8-3.1
Renal disease	73	4.4	2.8-7.0	74	4.2	2.6-6.6
Coronary bypass surgery	254	1.0	0.8-1.1	252	1.0	0.8-1.1
< 5 yrs	123	0.6	0.5-0.8	111	0.8	0.5-0.9
Percutaneous coronary intervention	134	0.4	0.3-0.5	174	0.6	0.5-0.7
< 5 yrs	88	0.7	0.5-1.1	91	1.0	0.6-1.6
Dobutamine stress echocardiography						
Wall motion abnormalities at rest	724	1.6	1.3-1.9	704	1.7	1.4-2.0
New wall motion abnormalities	608	1.1	0.9-1.36	604	1.3	1.0-1.6
BMI groups						
Underweight	69	2.4	1.7-3.6	58	2.1	1.5-3.1
Overweight	596	0.7	0.6-0.8	422	0.8	0.7-0.9
Obese	163	0.6	0.5-0.8	117	0.8	0.6-0.9

CHAPTER 2

The Obesity Paradox in Patients with Peripheral Arterial Disease

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The Obesity Paradox in Patients With Peripheral Arterial Disease

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Abstract

Background: Cardiac events are the predominant cause of late mortality in patients with peripheral arterial disease (PAD). In these patients, mortality decreases with increasing body mass index (BMI). COPD is identified as a cardiac risk factor, which preferentially affects underweight individuals. Whether or not COPD explains the obesity paradox in PAD patients is unknown.

Methods: We studied 2,392 patients who underwent major vascular surgery at one teaching institution. Patients were classified according to COPD status and BMIs (i.e., underweight, normal, overweight, and obese), and the relationship between these variables and all-cause mortality was determined using a Cox regression analysis. The median follow-up period was 4.37 years (interquartile range, 1.98 to 8.47 years).

Results: The overall mortality rates among underweight, normal, overweight, and obese patients were 54%, 50%, 40%, and 31%, respectively ($p < 0.001$). The distribution of COPD severity classes showed an increased prevalence of moderate-to-severe COPD in underweight patients. In the entire population, BMI (continuous) was associated with increased mortality (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.94 to 0.98). In addition, patients who were classified as being underweight were at increased risk for mortality (HR, 1.42; 95% CI, 1.00 to 2.01). However, after adjusting for COPD severity the relationship was no longer significant (HR, 1.29; 95% CI, 0.91 to 1.93).

Conclusions: The excess mortality among underweight patients was largely explained by the overrepresentation of individuals with moderate-to-severe COPD. COPD may in part explain the "obesity paradox" in the PAD population.

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Key words: Body Mass Index; Chronic Obstructive Pulmonary Disease; Mortality, Peripheral Arterial Disaese.

Abbreviations

ACE:	Angiotensin-converting enzyme
BMI**:**	Body mass index
DM:	Diabetes mellitus
HF:	Heart failure
HR**:**	Hazard ratio
CI**:**	Confidence interval
PAD:	Peripheral arterial disease

Introduction:

Cardiac events are the predominant cause of late mortality in patients with peripheral arterial disease (PAD).[1-3] Interestingly, in this population, unlike the situation in the general population, patients who are obese or overweight have better survival rates than those patients who are of normal weight.[4] Indeed, the greatest mortality rates are observed in patients who are underweight. This phenomenon has been referred to as the "obesity paradox".[4,5] To date, the reasons underlying the obesity paradox have not been fully elucidated. Over the past decade, COPD has emerged as an independent risk factor for cardiovascular mortality.[6,7] The effects of COPD on cardiovascular risk are amplified in the presence of another cardiac risk factor (e.g., smoking, hypercholesterolemia, or PAD).[8] In this study, we investigated the influence of COPD on the relationship between body mass index (BMI) and mortality in a group of patients with PAD.[9]

Methods

We studied 2,392 consecutive adult surgical patients who were admitted to the Department of Vascular Surgery of Erasmus University Medical Center (Rotterdam, the Netherlands) between January 1990 and November 2006. Patients were evaluated for the presence and severity of COPD prior to their surgical intervention using spirometry. Vascular surgical interventions included abdominal aortic surgery, carotid endarterectomy, or lower limb arterial revascularization procedures. BMI was measured during preoperative evaluation using standard procedures. Ethics approval for data collection and cohort evaluation were obtained from the Medical Ethics Committee of the hospital.

Baseline data included age, height, weight, and recorded medical history. The National Institutes of Health obesity classification[10] was used to divide the study population into the following four BMI categories: underweight (BMI <18.5 kg/m^2); normal weight (BMI, 18.5 to 24.9 kg/m^2); overweight (BMI, 25 to 29.9 kg/m^2); and obese (BMI ≥30 kg/m^2). The number of patients studied in each of these groups was 63 (2%), 1,101 (33%), 956 (28%), and 272 (8%), respectively. We differentiated the patients according to whether they had COPD (n=1,110; 46.4%) or did not have COPD (n=1,282; 53.6%) based on the definition of the Global Initiative for Chronic Obstructive Lung Disease (or GOLD) Committee (FEV_1/FVC ratio following therapy with bronchodilators and symptoms of cough or dyspnea, <70%). Mild COPD was defined as an FEV_1 of ≥80% predicted; moderate COPD was defined as an FEV_1 of ≥50% to <80% predicted; and severe COPD was defined as an FEV_1 of <50% predicted.[11] We considered patients without COPD as those without pulmonary function tests, those without symptoms (i.e., without pulmonary complaints and/or pulmonary medications), and those who had normal arterial blood gas levels (PCO_2 <6.4 kPa; PO_2 >10.0 kPa) at the time of assessment.

Cardiac medical history included details of previous myocardial infarction, angina pectoris, heart failure (HF), and coronary artery revascularization (i.e., percutaneous coronary intervention or coronary artery bypass grafting). Comorbidities reported in the medical history included diabetes mellitus (DM), hypertension, smoking, dyslipidemia, and renal dysfunction. DM was defined as a fasting glucose concentration of ≥7.0 mmol/L or the use of a hypoglycemic agent. Hypertension was defined as a BP of

≥140/90 mmHg or the use of antihypertensive medications. A diagnosis of HF was considered if the patient had a history of shortness of breath on exertion or at rest, decreased physical ability, swelling of lower limbs on physical examination, and echocardiographic signs consistent with cardiac decompensation.[12] Dyslipidemia was defined as a fasting serum total cholesterol level of ≥5.5 mmol/L, a triglyceride level of ≥1.7 mmol/L, or a high-density lipoprotein cholesterol level of ≤1.0 mmol/L at assessment or the use of lipid-lowering agents. Renal dysfunction was defined as a serum creatinine level of >2.0 mg/dL (177 μmol/L) or a requirement for dialysis. In addition, the cardiac risk score was determined for each patient using the Lee revised cardiac risk index, which included information about vascular operations, history of ischemic heart disease, HF, cerebrovascular accidents, insulin therapy for DM, and renal disease with a serum creatinine level of >2.0 mg/dL.[13] Patients were assessed for the use of cardiac medications including β-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors, diuretics, aspirin, anticoagulants, nitrates, and calcium channel blockers. The use of pulmonary medications, including bronchodilators and corticosteroids, was also captured.

Study End Points

The end of this study was all-cause mortality. The median duration of follow-up was 4.37 years (interquartile range, 1.98 to 8.47 years). Information about death was obtained and verified by reviewing the hospital record and linking with the national civil registry.

Statistical Analysis

Categoric variables are expressed as percentages and were compared using a Pearson χ^2 test. Continuous variables are presented as the mean (±SD) and were compared using analysis of variance. We performed univariate and multivariate analyses of survival times using a Cox proportional hazard model for all-cause mortality from which hazard ratios (HRs) and 95% confidence intervals (CIs) were derived. In the regression analyses, we used BMI both as a continuous variable and as a categoric variable. When the categoric BMI variable was included in the model, patients with normal weight were

taken as the reference group. In the multivariate models, we adjusted for baseline characteristics including age, gender, cardiac risk score, current smoking status, COPD severity, year of surgery, and use of pulmonary medications. In addition, we used stepwise regression models to investigate the association between the BMI categories and mortality, with stepwise adjustment made for clinical variables and subsequently for COPD severity and current smoking. Statistical significance was defined as a p value of <0.05. All statistical analysis was performed using a statistical software package (SPSS, version 15.0 for Windows; SPSS; Chicago, IL).

Results

In the population that we studied, we found a relatively homogenous distribution of BMI (mean BMI, 25.4±4.0 kg/m^2). Of the 2,392 patients, only 2.6% were underweight and 11.4% were obese, while the majority was either normal (46%) or overweight (40%). Patient characteristics according to BMI classifications are presented in Table 1. Current smokers were more prominent in the underweight group (p=0.002). Moderate-to-severe COPD was more frequent among underweight patients (40%), while the frequencies of COPD in the overweight and obese groups were 25% and 22%, respectively (p <0.001). In contrast to the underweight group, patients in the obese group had more cases of hypertension, DM, and dyslipidemia, and were more likely to be treated with β-blockers, statins, aspirin, and ACE inhibitors (p<0.05 for all). During follow-up, 1,048 patients (43.8%) died; 56.8% of them had COPD. Mortality among patients in different BMI categories included 34 patients (54%) in the underweight group, 550 patients (50%) in the normal group, 380 patients (40%) in the overweight group, and 83 patients (31%) in the obese group (p <0.001).

The relationships among BMI categories and COPD classifications are shown in Figure 1. The prevalence of COPD showed an inverse relationship with BMI; COPD was present more often in patients with lower BMI (p <0.001). The percentage of COPD was highest in patients who were underweight (51%), which was largely driven by the increased prevalence of severe COPD in this group. In the underweight category, 19% of the patients had severe COPD; whereas, in the obese category only 2% of the patients had severe COPD.

Moderate-to-severe COPD was independently associated with increased mortality (moderate COPD: HR, 1.67; 95% CI, 1.42 to 1.97; severe COPD: HR, 1.96; 95% CI, 1.50 to 2.55) [Table 2]. BMI, on the other hand, was inversely associated with mortality. The risk of mortality increased by 4% for each 1 kg/m^2 reduction in BMI. After adjusting for the cardiac risk score, age, gender, year of surgery, current smoking status, and use of pulmonary drugs, patients who were underweight were 1.42 times more likely to die than individuals of normal weight (HR, 1.42; 95% CI, 1.00 to 2.01). In contrast, overweight and obese individuals had a reduced risk of mortality (overweight patients: HR, 0.73; 95%

CI, 0.64 to 0.84; obese patients: HR, 0.68; 95% CI, 0.53 to 0.86) [Table 3, model 4]. When COPD severity was added to the multivariate model, the relationship between underweight status and mortality no longer remained statistically significant (HR, 1.29; 95% CI, 0.91 to 1.93). However, obesity and overweight remained significantly related to mortality (Table 3, model 5).

Discussion

In this study, we examined a large cohort of patients with PAD and found a high prevalence of COPD (46.4%), especially among patients who were underweight. We observed an inverse relationship between BMI and mortality, which is consistent with the obesity paradox described previously. However, when we adjusted for COPD and its severity, the relationship between underweight and mortality no longer remained significant, indicating that a substantial proportion of the excess deaths in patients with low BMI occur in subjects with COPD. This raises the possibility that the excess deaths in patients with low BMI are related to the patients' underlying COPD. Our results are in accordance with those of Landbo et al.[14] They studied the prognostic association of BMI in a similar population of COPD patients and observed that underweight patients, especially those with severe COPD, had an increased risk of mortality.

Since spirometry is generally not part of a normal preoperative assessment for patients who are undergoing major vascular surgery at many institutions, COPD may remain undiagnosed and untreated in this group of patients, resulting in excess morbidity and mortality. Indeed, even in our population, only 9% of the cohort was taking bronchodilators, though the overall prevalence of COPD was 47% and that for moderate-to-severe COPD was 27%. The findings in this study highlight the need for more aggressive use of spirometry and the institution of COPD interventions (including smoking cessation, treatment of exacerbations, and the use of maintenance drugs) for patients with peripheral vascular disease.

The mechanisms responsible for the inverse relationship between BMI and mortality are uncertain. Previous studies[15,16] have suggested that underweight patients demonstrate a higher

metabolic rate, lower antioxidant capacity in skeletal muscles, and increased systemic inflammatory responses, which may contribute to excess weight loss and morbidity. Underweight status has also been associated with overt or occult malignancy. Our study findings suggest that in addition to the above factors, COPD may also be responsible for the obesity paradox (in the low BMI categories).

Our finding that overweight and obesity are associated with improved survival is consistent with the obesity paradox of survival in HF patients. Previous studies have clearly demonstrated that HF patients who have a higher percentage of body fat[17,18] and elevated BMI[19,20] have lower mortality than those with normal or reduced BMIs. However, the mechanism responsible for this observation remains elusive.[21,22] Some investigators have suggested[23-25] that increased BMI may confer protection against endotoxin and inflammatory cytokines by increasing the production of "buffering" lipoproteins. HF may be diagnosed in obese patients at an earlier stage because they tend to be more symptomatic than HF patients with lean body mass. Thus, obesity may simply be a marker for less severe HF.

Our finding that nearly 50% of patients undergoing major vascular surgery for PAD had COPD highlights the importance of using screening spirometry in this population. Over half of these patients in the underweight category had moderate-to-severe COPD. These data support the notion of more aggressive "screening" and treatment for COPD before and after surgery to optimize the health outcomes of these patients.

There were certain limitations to the study. BMI has been recently questioned as a sensitive measure of body fatness.[26] Other anthropometric measurements of body fat such as waist circumference were not routinely performed preoperatively and, hence, could not be included in our analysis. We also did not have complete lung function measurements for the cohort. Knowledge regarding total lung and inspiratory capacity as well as diffusing capacity may provide incremental information on mortality. Moreover, because we did not directly interview patients, we could not separate out purposeful from nonpurposeful weight loss.[27] Thus, the underlying reasons for the low BMI in our population are unknown. Finally, because smoking is a more powerful risk factor in PAD patients

than in patients with HF, ischemic heart disease, or stroke, it is uncertain whether our current findings can be generalized to other cardiovascular populations.

Conclusion

We found that nearly 50% of patients with PAD undergoing a surgical procedure had evidence of COPD and that BMI was inversely related to long-term mortality. Importantly, there was a disproportionate overrepresentation of COPD in patients with low BMI. Patients with low BMI had an increased risk of mortality, while obese and overweight patients had a reduced risk of mortality compared to individuals of normal weight. Adjustments for the severity of COPD abolished the significant relationship between BMI and mortality in those patients who were underweight, but not in those who were overweight or obese. These data suggest that COPD is a highly prevalent condition in PAD patients who are undergoing surgical procedures, and that COPD may be responsible for the obesity paradox associated with reduced BMI and mortality in patients with PAD.

References:

1. Thatipelli MR, Pellikka PA, McBane RD, et al. Prognostic value of ankle-brachial index and dobutamine stress echocardiography for cardiovascular morbidity and all-cause mortality in patients with peripheral arterial disease. J Vasc Surg 2007; 46:62-70

2. Lee AJ, Price JF, Russell MJ, et al. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation 2004; 110:3075-3080

3. Doonan AL, Karha J, Carrigan TP, et al. Presence of carotid and peripheral arterial disease in patients with left main disease. Am J Cardiol 2007; 100:1087-1089

4. Galal W, van Domburg RT, Feringa HH, et al. Relation of body mass index to outcome in patients with known or suspected coronary artery disease. Am J Cardiol 2007; 99: 1485-1490

5. Uretsky S, Messerli FH, Bangalore S, et al. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med 2007; 120:863-870

6. Sachdev M, Sun JL, Tsiatis AA, et al. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. J Am Coll Cardiol 2004; 43:576-582

7. Sin DD, Anthonisen NR, Soriano JB, et al. Mortality in COPD: role of comorbidities. Eur Respir J 2006; 28:1245-1257

8. Engstrom G, Hedblad B, Valind S, et al. Increased incidence of myocardial infarction and stroke in hypertensive men with reduced lung function. J Hypertens 2001; 19:295-301

9. Johannessen A, Omenaas ER, Bakke PS, et al. Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. Thorax 2005; 60:842-847

10. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Am J Clin Nutr 1998; 68:899-917

11. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary Am J Respir Crit Care Med 2007; 532-555

12. Braunwald E. Heart failure. In: Zipes DP, Libby P, Bonow RO, et al, eds. Braunwald's heart disease: a textbook of cardiovascular medicine. 7th ed. Philadelphia, PA: Elsevier Saunders, 2005; 603-624

13. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043-049

14. Landbo C, Prescott E, Lange P, et al. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 160:1856-1861

15. Stump CS, Henriksen EJ, Wei Y, et al. The metabolic syndrome: role of skeletal muscle metabolism. Ann Med 2006; 38:389-402

16. Imbeault P, Tremblay A, Simoneau JA, et al. Weight loss-induced rise in plasma pollutant is associated with reduced skeletal muscle oxidative capacity. Am J Physiol Endocrinol Metab 2002; 282:E574-E549

17. Lavie CJ, Osman AF, Milani RV, et al. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. Am J Cardiol 2003; 91:891-894

18. Lavie CJ, Milani RV, Artham SM, et al. Does body composition impact survival in patients with advanced heart failure [abstract]? Circulation 2007; 116:II_360 (abstract 1713)

19. Lavie CJ, Mehra MR, Milani RV. Obesity and heart failure prognosis: paradox or reverse epidemiology? Eur Heart J 2005; 26:5-7

20. Horwich TB, Fonarow GC, Hamilton MA, et al. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2001; 38:789-795

21. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, et al. Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care 2007; 10:433-442

22. Horwich TB, Fonarow GC. Reverse epidemiology beyond dialysis patients: chronic heart failure, geriatrics, rheumatoid arthritis, COPD, and AIDS. Semin Dial 2007; 20:549-553

23. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. Lancet 2000; 356:930-933

24. Szmitko PE, Teoh H, Stewart DJ, et al. Adiponectin and cardiovascular disease: state of the art? Am J Physiol Heart Circ Physiol 2007; 292:H1655-H1663

25. Lavie CJ, Milani RV, Ventura HO. Obesity, heart disease, and favorable prognosis: truth or paradox? Am J Med 2007; 120:825-826

26. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Diag- nostic performance of body mass index to detect obesity in patients with coronary artery disease. Eur Heart J 2007; 28:2087-2093

27. Schols AM, Slangen J, Volovics L, et al. Weight loss is a reverse factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157(6 Pt 1): 1791-1797

Figure titles and legends:

Figure 1: The cross-relationship between COPD status and BMI in our population: *COPD classifications among BMI categories*

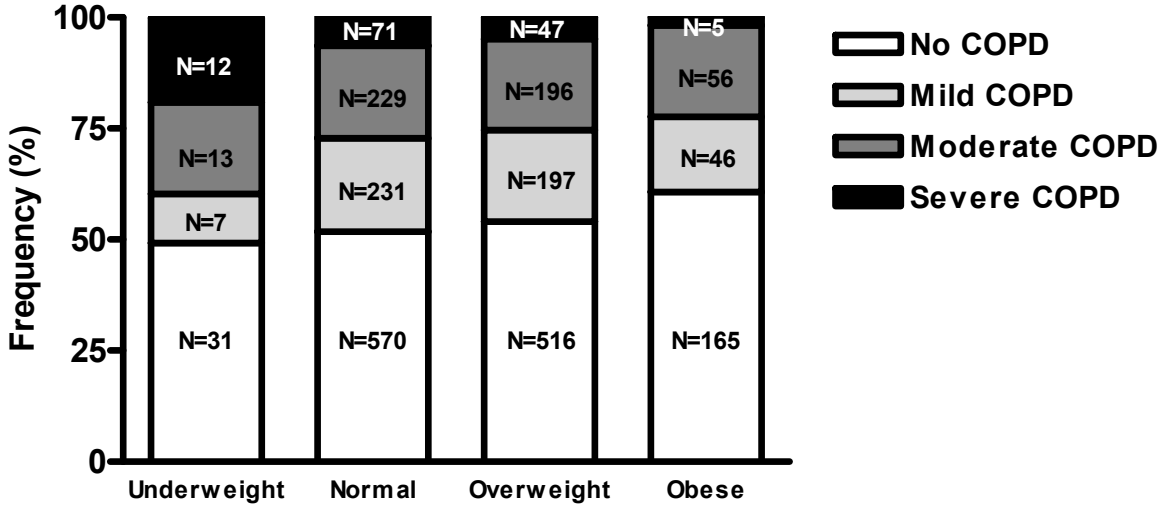

Table 1. The Baseline Clinical Characteristics of 2392 Patients According to Body Mass Index (BMI) Categories.

	Total (n=2392)	Underweight group (n=63)	Normal weight group (n=1101)	Overweight group (n=956)	Obese (n=272)	P-value
Demographics						
Mean age, year (SD)	66 (11)	64 (14)	67 (11)	67 (10)	63 (11)	<0.001
Male gender (%)	1782 (75)	34 (54)	823 (75)	749 (78)	176 (65)	<0.001
Type of surgery (%)						<0.001
AAA[1]	966 (40)	27 (43)	456 (41)	405 (42)	78 (29)	
CEA[2]	561 (24)	6 (10)	217 (20)	254 (27)	84 (31)	
LLR[3]	865 (36)	30 (47)	428 (39)	297 (31)	110 (40)	
Cardiac history (%)						
Myocardial infarction	618 (26)	11 (18)	288 (26)	253 (27)	66 (24)	0.41
Revascularisation[4]	458 (19)	11 (18)	196 (18)	206 (22)	44 (16)	0.09
Heart failure	133 (6)	1 (2)	76 (7)	41 (4)	15 (6)	0.04
Angina	419 (18)	9 (14)	182 (17)	175 (18)	53 (20)	0.51
Clinical variables (%)						
Hypertension	1042 (44)	10 (16)	442 (40)	449 (47)	141 (52)	<0.001
Diabetes Mellitus	362 (15)	0 (0)	127 (12)	155 (16)	80 (29)	<0.001
Current smoker	781 (33)	26 (41)	395 (36)	288 (30)	72 (27)	0.002
Dyslipidemia	520 (22)	6 (10)	208 (19)	236 (25)	70 (26)	<0.001
Mean BMI (SD)	25 (4)	17 (1)	23 (2)	27 (1)	33 (4)	<0.001
Renal dysfunction	192 (8)	8 (13)	94 (9)	67 (7)	23 (9)	0.30
COPD						<0.001
No	1282 (53)	31 (49)	570 (52)	516 (54)	165 (61)	
Mild	481 (20)	7 (11)	231 (21)	197 (21)	46 (17)	
Moderate	494 (21)	13 (21)	229 (21)	196 (20)	26 (20)	
Severe	135 (6)	12 (19)	71 (6)	47 (5)	5 (2)	
Cardiac medication (%)						
Statins	719 (30)	12 (19)	298 (27)	315 (33)	94 (35)	0.02
Beta-blockers	1026 (43)	15 (24)	457 (42)	408 (43)	146 (54)	<0.001
ACE-inhibitors	640 (27)	11 (18)	264 (24)	278 (29)	87 (32)	0.004
Calcium antagonists	602 (25)	12 (19)	271 (25)	242 (25)	77 (28)	0.41
Diuretics	502 (21)	10 (16)	218 (20)	214 (22)	60 (22)	0.36
Aspirin	1021 (43)	18 (29)	434 (39)	432 (45)	137 (50)	<0.001
Anti-coagulants	937 (39)	30 (48)	431 (39)	375 (39)	101 (37)	0.50
Nitrates	307 (13)	6 (10)	134 (12)	129 (14)	38 (14)	0.63
Pulmonary medication (%)						
Bronchodilators	205 (9)	8 (13)	98 (9)	78 (8)	21 (8)	0.58
Corticosteroids	308 (13)	10 (16)	150 (14)	117 (12)	31 (11)	0.59

[1]Abdominal aortic surgery
[2]Carotid endarterectomy
[3]Lower limb arterial reconstruction
[4]Previous coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)
Continuous variables are shown as mean (SD), while dichotomous variables are shown as number (% of column totals)
[Ω] BMI values expressed as kg/m**²**.

Table 2. The Relationship between Baseline Risk Factors and All-Cause Mortality.

	Univariate analysis				Multivariate analysis [§]		
Variables	HR	95% CI	P value		HR	95% CI	P value
COPD [φ]							
Mild	1.45	1.23-1.71	<0.001		1.18	1.00-1.40	0.053
Moderate	2.21	1.91-2.56	<0.001		1.67	1.42-1.97	<0.001
Severe	2.52	1.99-3.18	<0.001		1.96	1.50-2.55	<0.001
BMI	0,95	0.94-0.97	<0.001		0.96	0.94-0.98	<0.001

[§] Adjustments were made for the Lee's revised cardiac risk score, age, gender, year of surgery and use of pulmonary drugs

[φ] Classification of COPD done according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. [11]

Table 3 Association between BMI (continuous and categories) and COPD severity and mortality

Variables	Model 1	Model 2	Model 3	Model 4	Model 5
Cases, No.	2387	2387	2387	2387	2387
Patients alive, No.	1340	1340	1340	1340	1340
BMI	0.95 (0.94-0.97)	0.95 (0.94-0.97)	0.96 (0.94-0.97)	0.96 (0.94-0.97)	0.96 (0.94-0.97)
Underweight	1.38 (0.98-1.96)	1.44 (1.02-2.04)	1.30 (0.92-1.40)	1.42 (1.00-2.01)	1.29 (0.91-1.93)
Overweight	0.73 (0.64-0.83)	0.73 (0.64-0.83)	0.73 (0.64-0.84)	0.73 (0.64-0.84)	0.74 (0.65-0.84)
Obese	0.68 (0.54-0.85)	0.67 (0.53-0.85)	0.67 (0.53-0.85)	0.68 (0.53-0.86)	0.68 (0.54-0.86)
Mild COPD	1.19 (1.01-1.41)		1.19 (1.00-1.41)		1.18 (1.00-1.40)
Moderate COPD	1.81 (1.55-2.10)		1.69 (1.43-1.99)		1.67 (1.42-1.97)
Severe COPD	2.11 (1.67-2.68)		1.97 (1.51-2.57)		1.96 (1.50-2.55)

Model 1: Age and gender adjusted
Model 2: Multivariate in which age, gender, cardiac risk score, year of surgery and pulmonary medication were adjusted for
Model 3: Multivariate in which all the variables in model 2 plus COPD severity were adjusted for
Model 4: Multivariate in which all the variables in model 2 plus cigarette smoking were adjusted for
Model 5: Multivariate in which all the variables in model 2 plus cigarette smoking and COPD severity were adjusted for

CHAPTER 3

Impact of obesity on postoperative and long-term outcomes in a general surgery population: a retrospective cohort study

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The Impact of Obesity on Postoperative and Long-term Outcome in a General Surgery Population: A Retrospective Cohort Study

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Mini-Abstract

The obesity paradox is evaluated retrospectively in a general surgery population. Both 30-day postoperative and long-term survival, including cause-specific mortality, is demonstrated in different BMI categories.

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Obesity paradox in general surgery

Abstract

Objective: To evaluate the presence of the obesity paradox in a general surgery population, reporting both postoperative and long-term survival, including cause-specific mortality.

Background: The obesity paradox has been demonstrated postoperatively in several surgical populations. However, only few studies reported long-term outcome.

Methods: This retrospective study included 10,427 patients scheduled for elective, non-cardiac surgery. Patients were classified as underweight (BMI < 18.5 kg/m^2); normal weight (BMI 18.5 - 24.9 kg/m^2); overweight (BMI 25.0 - 29.9 kg/m^2); obesity class I (BMI 30.0 - 34.9 kg/m^2); obesity class II (BMI 35.0 - 39.9 kg/m^2); and obesity class III (BMI ≥ 40.0 kg/m^2). Study endpoints were 30-day postoperative and long-term mortality, including cause-specific mortality. Multivariate analyses were used to evaluate mortality risks in different BMI categories.

Results: Within 30-days after surgery, 353 (3.4%) patients died. Only overweight was associated with postoperative mortality, showing improved survival (OR 0.7; 95% CI 0.6-0.9). During the long-term follow-up 4884 (47%) patients died. Underweight patients had the highest mortality risk (HR 1.5; 95% CI 1.3-1.7), particularly caused by high cancer related mortality. In contrast, overweight and obese patients demonstrated improved survival (overweight: HR 0.8; 95% CI 0.7–0.8; obesity class I: HR 0.7; 95% CI 0.6–0.8; obesity class II: HR 0.6; 95% CI 0.5-0.8; obesity class III: HR 0.7; 95% CI 0.5-0.9), mainly because of a strongly reduced risk of cancer related mortality.

Conclusions: In this surgical population the obesity paradox could be validated at long-term, mainly because of decreased cancer related mortality among the obese.

Introduction

Overweight and obesity are major health conditions that currently affect more than two-thirds of the US population, and the prevalence of obesity still continues to increase.[1, 2] In Europe obesity has also reached epidemic proportions, although there are large differences between European countries.[3]

The obesity epidemic also affects surgery, not merely because of an increase in obese patients, but also because of an increase in obesity related disorders that require surgery.[4, 5] Despite the medical hazards associated with obesity,[5] recent literature has demonstrated that obese patients show improved survival, a phenomenon referred to as the *obesity paradox*. The obesity paradox has been described in various populations, including the general population,[6] and in patient populations with heart failure,[7] coronary artery disease [8] and dialysis,[9] among others. Moreover, several surgical populations have shown a similar survival benefit for the obese patient in the postoperative period.[10-13] However, the majority of these studies included specific surgical populations, and did not report long-term survival.

Therefore, this study was undertaken to evaluate the presence of the obesity paradox in a general surgery population, reporting both postoperative and long-term outcome, including cause-specific mortality.

Methods

Study Design and Patients

This retrospective study included 10,427 patients who underwent non-cardiac surgery between January 1991 and December 2008, in the Erasmus Medical Center, Rotterdam, the Netherlands. In all patients, height and weight measurements were obtained during preoperative evaluation at the anesthesia clinic. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Baseline clinical data were retrieved from medical records and included age, gender, ischemic heart disease (history of myocardial infarction or angina pectoris), heart failure, cerebrovascular disease (history of cerebrovascular accident and/or transient ischemic attack), diabetes mellitus (treatment with insulin and/or fasting blood glucose ≥ 7 mmol/L), renal dysfunction (serum creatinine > 2.0 mg/dL), chronic obstructive pulmonary disease (COPD), and smoking status.

Classifications and Risk Stratification

The World Health Organization (WHO) classification was used to divide the patient population into the following BMI categories: underweight (BMI < 18.5 kg/m^2); normal weight (BMI 18.5 – 24.9 kg/m^2); overweight (BMI 25.0 – 29.9 kg/m^2); obese (BMI ≥ 30.0 kg/m^2), further divided in obesity class I (mild obesity: BMI 30.0 -34.9 kg/m^2); obesity class II (moderate obesity: BMI 35.0 -39.9 kg/m^2); and obesity class III (morbid obesity: BMI ≥ 40.0 kg/m^2).[14]

Based on the guidelines of the European Society of Cardiology,[15] the non-cardiac surgical procedures were classified into expected low cardiac risk (breast, dental, endocrine, eye, gynecology, orthopedic and reconstructive), intermediate

cardiac risk (abdominal, carotid, endovascular aneurysm, head and neck, neurologic, pulmonary, renal, urologic, and remaining), and high cardiac risk (aortic, peripheral vascular and other vascular).

The Revised Cardiac Risk Index (RCRI), which is used to identify surgical patients at the highest risk for cardiovascular events, was determined for every patient. The RCRI assigns one point to each of the following characteristics: high-risk surgery, diabetes mellitus, renal dysfunction, ischemic heart disease, heart failure, and cerebrovascular disease.[16]

Study Endpoints

The primary endpoints were 30-day postoperative mortality and long-term mortality. Length of hospital stay (LOS) was described as a secondary outpoint. Median follow-up duration was 5.4 years (interquartile range 2.2 – 9.7 years). Survival status was obtained from the hospital records and the civil registries. In 74 patients follow-up was missing (0.7%). Cause of death was classified as cardiovascular, cancer or other (non-cardiovascular, non-cancer), and was ascertained by examining medical records and autopsy reports. For patients without a definite cause of death, an assumption was made based on prior history. If prior history showed no significant morbidities, cause of death was classified as 'unknown' (6.6%). Cardiovascular mortality was defined as any death with a cerebro-cardiovascular cause and included death following myocardial infarction, cardiac arrhythmias, congestive heart failure, stroke and sudden unexpected death. Non-cardiovascular, non-cancer mortality included respiratory, infectious and other causes.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical data as numbers and percentages. Continuous variables showing a normal distribution were compared using analysis of variance; otherwise, the Kruskal-Wallis and Mann-Whitney *U* test were applied. Categorical data were compared with chi-squared tests.

Data on smoking status were available in 8887 (85%) patients and preoperative pulmonary function testing was performed in 9953 (96%) patients, which was used to identify patients with COPD. Missing value analysis was used to impute the missing data on smoking status (n=1540) and COPD (n=474). Regression substitution was performed to predict the values for smoking and COPD, using other variables without missing values (age, gender, height, weight, myocardial infarction, angina pectoris, heart failure, cerebrovascular accident, diabetes mellitus, and renal dysfunction) and available data on smoking status and COPD.

Logistic regression analysis was used to study the association between BMI category and 30-day postoperative outcomes. Long-term mortality risk was evaluated using a Cox proportional hazard model. When the categorical BMI variable was included in the model, patients with normal BMI were taken as the referent group. Multivariate analyses were primarily adjusted for predefined potential confounders (age, gender, RCRI, COPD and smoking status, surgery risk, and year of surgery). Cumulative long-term survival was determined by the Kaplan-Meier method and compared with the log-rank test.

Sensitivity analyses were performed in patients without missing values for smoking and COPD. Furthermore, to limit effects of pre-existing disease on

baseline BMI, sensitivity analyses were performed excluding all person-years and deaths in the first 5 years of follow-up.[17]

For all tests, a 2-sided p-value of < 0.05 was considered significant. All statistical analyses were performed using a statistical software package (SPSS, version 17.0 for Windows, SPSS Inc., Chicago, Ill).

Results

The study population consisted of 10,427 non-cardiac surgery patients. According to the BMI categories, 475 (5%) patients were classified as underweight, 4,601 (44%) as normal weight, 3,500 (34%) as overweight, 1,851 (18%) as obese, with 1,311 (13%) patients with obesity class I, 368 (4%) patients with obesity class II, and 172 (2%) patients with obesity class III, respectively. Patient characteristics according to BMI classification are shown in Table 1. The BMI among the study population attained a normal distribution, with a mean BMI of 25.8 (± 5.2) kg/m^2. Mean age of the study population was 58 (± 16) years and 59% were men. Underweight and obese class III patients were younger, whereas overweight patients were older than patients with a normal BMI. Gender also varied significantly by BMI category, with the underweight and obese patients more often being females, and overweight patients more often being males ($p<0.001$).

Medical history revealed that the prevalence of diabetes mellitus increased from 30% in the lowest- to 49% in the highest BMI category ($p<0.001$). Furthermore, ischemic heart disease and cerebrovascular disease were more common in the overweight and obese class I and class II patients, with a prevalence of > 10% for angina pectoris and 7% for cerebrovascular disease

(p<0.001 and p 0.005 respectively). On the other hand, smoking prevalence was highest in the underweight group (52%) (p<0.001).

The majority (62%) of surgical procedures were classified as intermediate cardiac risk (Table 2). Low-risk surgery was most often carried out in obese class II and III patients (40%), whereas high-risk surgery was most often performed in overweight patients (16%) (p<0.001).

Postoperative mortality differed between the BMI categories. Within 30-days after surgery, a total of 353 (3.4%) patients died. Underweight patients had the highest 30-day mortality rate (4.5%), compared to lower rates in the overweight (3.0%), obesity class I (3.1%), obesity class II (3.0%) and obesity class III patients (2.9%), although this difference was not significant (p=0.284). After adjusting for potential confounders (age, gender, RCRI, COPD and smoking status, surgery risk, and year of surgery), overweight patients showed a reduced postoperative mortality risk (OR 0.7; 95% CI 0.6-0.9), whereas other BMI categories showed no association with postoperative mortality risk (Figure 1).

The LOS also varied significantly by BMI category. The median LOS was 7.0 days (IQR 2.0-15.0 days) for normal weight patients, and 7.0 days (IQR 2.0-16.0 days) for underweight patients (p=0.7). However, LOS was significantly shorter for overweight and obese patients, compared to normal weight patients (overweight: median LOS 6.0 days (IQR 2.0-13.0) (p=0.001); obesity class I: median LOS 5.0 days (IQR 1.0-12.0 days) (p<0.001); obesity class II: median LOS 4.0 days (IQR 1.0-9.0) (p<0.001); obesity class III: median LOS 4.0 days (IQR 1.0-10.0 days) (p<0.001); respectively). When the analysis was stratified by surgical risk, LOS was shorter for obese patients compared to normal weight patients, particularly in intermediate risk surgery (p<0.001) and high-risk surgery,

although this difference was not significant (p=0.06). On the other hand, in low-risk surgery LOS did not differ between BMI categories (p=0.5).

During the long-term follow-up, 4884 (47%) patients died. Mortality rates varied significantly among BMI categories: 276 (58%) patients in the underweight category; 2361 (52%) patients in the normal weight category; 1606 (46%) patients in the overweight category; 481 (37%) patients in the obese class I category; 115 (31%) patients in the obese class II category; and 45 (27%) patients in the obese class III category (p<0.001) (Figure 4 and Table 3). Cumulative long-term survival according to BMI category is demonstrated in Figure 2 (log rank p<0.001). Multivariate regression analyses, adjusting for age, gender, RCRI, COPD and smoking status, surgery risk, and year of surgery, demonstrated that in underweight patients all-cause mortality risk was increased (adjusted HR 1.5; 95% CI 1.3–1.7), whereas overweight and obese patients showed improved survival (overweight: adjusted HR 0.8; 95% CI 0.7–0.8; obesity class I: adjusted HR 0.7; 95% CI 0.6–0.8; obesity class II: adjusted HR 0.6; 95% CI 0.5-0.8; obesity class III: adjusted HR 0.7; 95% CI 0.5-0.9, respectively) (Table 3).

Sensitivity analyses in patients without missing values on smoking and COPD did not change these hazard ratios. However, sensitivity analyses excluding the first 5 years of follow-up yielded different results. In underweight patients mortality risk was still increased (adjusted HR 1.4; 95% CI 1.1-1.8), and overweight and obesity class I remained associated with improved survival (adjusted HR 0.9; 95% CI 0.8-1.0; and adjusted HR 0.8; 95% CI 0.7-1.0; respectively). On the other hand, obesity classes II and III were no longer associated with mortality (obesity class II: adjusted HR 0.8; 95% CI 0.6-1.1; obesity class III: adjusted HR 1.3; 95% CI 0.8-2.0).

Cause-specific mortality among the BMI categories is represented in Figure 4. Cardiovascular mortality accounted for 22% of deaths in underweight patients, and this increased to 42% in obesity class III patients (p=0.001). Despite the high cardiovascular mortality in the overweight and obese patients, multivariate analyses did not show independent associations with BMI and cardiovascular mortality risk (Table 3).

Cancer related death was responsible for the majority (52%) of deaths in underweight patients, and this decreased to 24% in obesity class III patients ($p < 0.001$). Underweight patients were 1.6 times more likely to die from cancer than normal weight patients (adjusted HR 1.6; 95% CI 1.3–1.9) (Table 3). In contrast, overweight and obese patients had a 30-70% reduced risk of cancer related mortality (overweight: adjusted HR 0.7; 95% CI 0.7-0.8; obesity class I: adjusted HR 0.5; 95% CI 0.4-0.6; obesity class II: adjusted HR 0.5; 95% CI 0.3-0.7; obesity class III: adjusted HR 0.3; 95% CI 0.2-0.6, respectively) (Table 3).

Discussion

In this large sample of general surgery patients from a single Dutch hospital, only overweight was associated with 30-day postoperative mortality, showing improved survival, whereas obesity was not associated with postoperative mortality. However, long-term survival was significantly better for obese patients, clearly showing the presence of the obesity paradox in this surgical population. Furthermore, cause-specific mortality differed significantly between BMI categories, with cardiovascular mortality accounting for more than one third of deaths in overweight and obesity, and cancer being responsible for the majority of deaths in underweight patients.

Postoperative mortality risk was not associated with obesity in our study, and was even reduced in overweight patients. Postoperative complications, like wound infections, are related to obesity and can lead to a longer hospital stay,[11, 12] however, they do not affect survival. Although this study did not assess surgical complications, hospital stay was shorter in patients with obesity classes I and II. Mullen et al. reported similar postoperative outcomes for the overweight and the obese, including lower mortality risks and reduced length of stay.[12] Increased awareness of the hazards of obesity by both surgeons and anesthesiologists,[18, 19] in combination with a decline in the prevalence of cardiovascular risk factors among the obese,[20] might have led to improved perioperative care and lower postoperative (cardiac) complication rates. These improvements can be reflected by reduced length of hospital stay and no additional mortality risk for the obese patient.

Although the current study did not demonstrate the obesity paradox at 30-day postoperatively, its presence could be confirmed at long-term. One of the hypotheses to explain the obesity paradox in our study might be that a decrease in cardiovascular related mortality, similar to observations in the general population[21], might have led to a decrease in all-cause mortality. Although the prevalence of cardiovascular risk factors and disease, including diabetes and ischemic heart disease, was high among the overweight and the obese, no independent association with cardiovascular mortality could be demonstrated. One of the explanations could be that the number of obese patients dying from cardiovascular causes was too small for meaningful subgroup analyses. However, considering that cardiovascular mortality was the leading cause of long-term mortality among the obese, this hypothesis might be less likely to explain the obesity paradox in the present study. Therefore, other explanations are probably

warranted to explain the obesity paradox in our surgical population, which is mainly determined by decreased cancer related deaths among the obese.

One of the explanations could be that obese oncology patients are not, or less often, referred for surgery, leading to selection bias and supposed improved survival. In addition, although several site-specific cancers are associated with obesity,[22] particularly with visceral adiposity,[23] BMI cannot distinguish between visceral and peripheral adiposity. Visceral adiposity is less common in pre-menopausal women.[23] Therefore, visceral adiposity might have been less prevalent among the predominantly female obese patients in our study, particularly in obese class III patients, leading to a lower prevalence of cancer. Another hypothesis is that overweight and obese patients had less disseminated cancer, as some studies have reported,[12, 24] in that way leading to improved survival.

Although obesity is associated with several cancers, Calle et al. demonstrated an inverse association between overweight and obesity and death from lung cancer.[25] Decreased mortality rates from lung cancer could have reduced total cancer mortality rates among the overweight and obese in the present study. However, similar to the current study, the population studied by Calle et al. included smokers. Smoking can be a potential confounder, because it is associated with both a decreased weight and an increased mortality risk.[17] Furthermore, smoking is related to an increased incidence of cancer. The effects of smoking on mortality cannot be separated from the effects of BMI on mortality in smoking-related diseases, like lung cancer.

Besides smoking associated weight loss, chronic diseases can also cause weight loss. Chronic diseases that cause weight loss may remain unnoticed for months or even years, for example in the case of cancer and COPD. Consequently, *reverse causation*, which means that lower weight is not a cause but a result of

chronic diseases that are related to poor outcome, can be another confounder associated with mortality.[17] In order to limit the effects of smoking and reverse causation on mortality risks, deaths occurring in the first years of follow-up should be disregarded, and analyses should be restricted to persons without prior disease and to persons who never smoked.[17] In the study by Calle et al. the apparent inverse association between obesity and lung cancer mortality risk disappeared after restricting analyses to persons who never smoked.

In the present study, the prevalence of smoking was higher in the underweight population compared to other BMI categories. This could offer another explanation for the obesity paradox in this surgical population. Underweight patients displayed the worst long-term survival, with nearly 60% mortality during follow-up. Furthermore, more than half of deaths were attributable to cancer. After exclusion of the first 5 years of follow-up, in order to limit the effects of pre-existing disease on baseline BMI, the obesity paradox was still present, with highest mortality risk in the underweight and improved survival in the overweight and obesity class I. Unfortunately, in the present study analyses could not be restricted to persons without prior disease and never smokers, since information regarding cancer diagnosis and former smoking was not available.

Several limitations of the present study have already been mentioned, including the inability of BMI to differentiate between visceral and peripheral adiposity, missing information on baseline cancer diagnosis and metastatic disease, and the unfeasibility to divide non-smokers into former and never smokers. In addition, information regarding medication use was not available. Furthermore, this is a retrospective observational study, and therefore causality between BMI and outcome cannot be established. Finally, data on smoking and COPD were incomplete. These patients were not excluded to prevent any bias, and

established statistical methods were used to impute missing values. It was assuring that in sensitivity analyses excluding patients with missing values, reported hazard ratios did not change.

In conclusion, in this large retrospective study of general surgery patients, postoperative mortality risk was reduced in overweight, and not associated with other BMI categories. At long-term the obesity paradox could be validated. Cardiovascular mortality remained the leading cause of mortality among the obese, whereas cancer related death was significantly decreased among the overweight and the obese.

References

1. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006; 295:1549-1555.

2. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 2010; 303:235-241.

3. Berghofer A, Pischon T, Reinhold T, et al. Obesity prevalence from a European perspective: a systematic review. *BMC Public Health*. 2008; 8:200.

4. Hawn MT, Bian J, Leeth RR, et al. Impact of obesity on resource utilization for general surgical procedures. *Ann Surg*. 2005; 241:821-826.

5. Haslam DW, James WP. Obesity. *Lancet*. 2005; 366:1197-1209.

6. Flegal KM, Graubard BI, Williamson DF, et al. Excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2005; 293:1861-1867.

7. Oreopoulos A, Padwal R, Kalantar-Zadeh K, et al. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J*. 2008; 156:13-22.

8. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. 2006; 368:666-678.

9. Kalantar-Zadeh K, Kopple JD. Obesity paradox in patients on maintenance dialysis. *Contrib Nephrol*. 2006; 151:57-69.

10. Oreopoulos A, Padwal R, Norris CM, et al. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring)*. 2008; 16:442-450.

11. Mullen JT, Davenport DL, Hutter MM, et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. *Ann Surg Oncol*. 2008; 15:2164-2172.

12. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg*. 2009; 250:166-172.

13. Davenport DL, Xenos ES, Hosokawa P, et al. The influence of body mass index obesity status on vascular surgery 30-day morbidity and mortality. *J Vasc Surg*. 2009; 49:140-147.

14. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000; 894:i-xii, 1-253.

15. Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J*. 2009; 30:2769-2812.

16. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999; 100:1043-1049.

17. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med*. 1999; 341:427-434.

18. De Hert S, Imberger G, Carlisle J, et al. Preoperative evaluation of the adult patient undergoing non-cardiac surgery: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2011; 28:684-722.

19. Buchwald H, Estok R, Fahrbach K, et al. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery*. 2007; 142:621-632.

20. Gregg EW, Cheng YJ, Cadwell BL, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA*. 2005; 293:1868-1874.

21. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet*. 1999; 353:1547-1557.

22. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008; 371:569-578.

23. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. *Diabetol Metab Syndr*. 2011; 3:12.

24. Tokunaga M, Hiki N, Fukunaga T, et al. Better 5-year survival rate following curative gastrectomy in overweight patients. *Ann Surg Oncol*. 2009; 16:3245-3251.

25. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003; 348:1625-1638.

Figures

Fig. 1 Adjusted odds ratios for 30-day postoperative mortality according to BMI body mass index categories

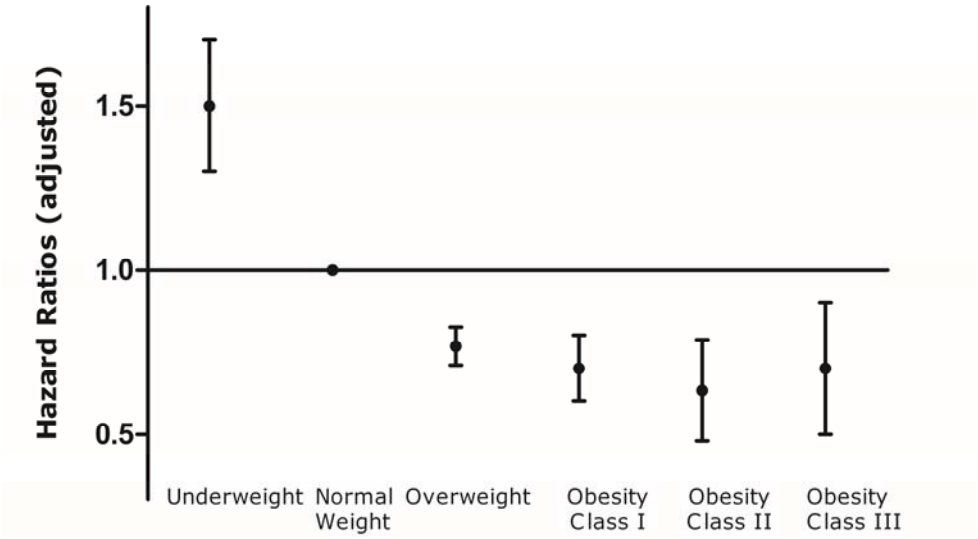


Fig. 2 Kaplan-Meier curves for long-term survival according to BMI categories

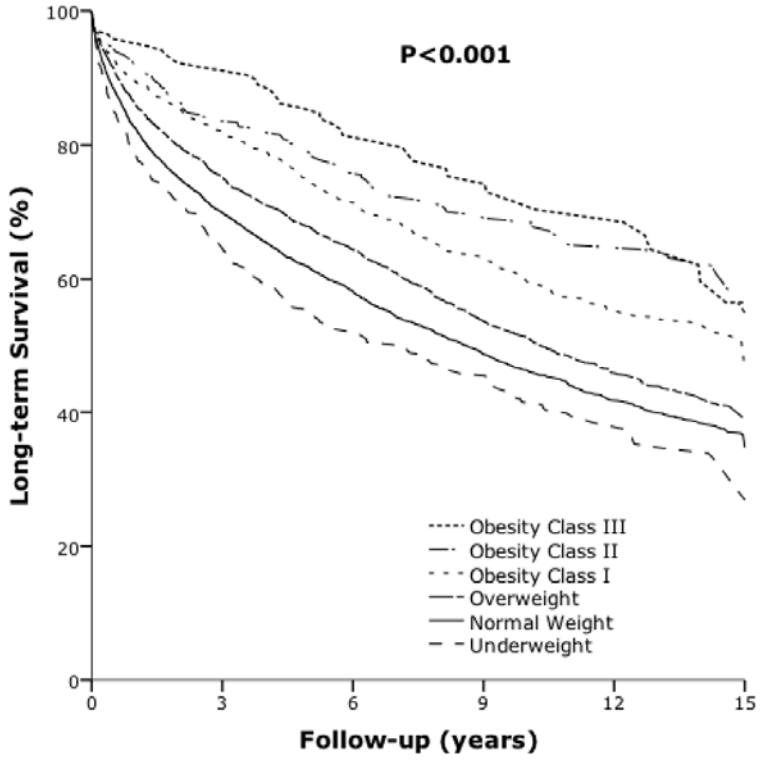


Fig. 3 Adjusted hazard ratios for long-term mortality according to BMI categories

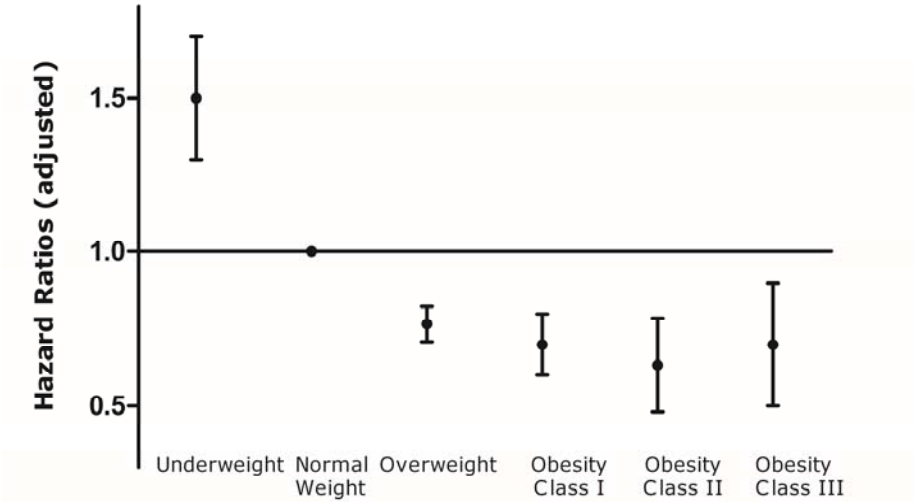
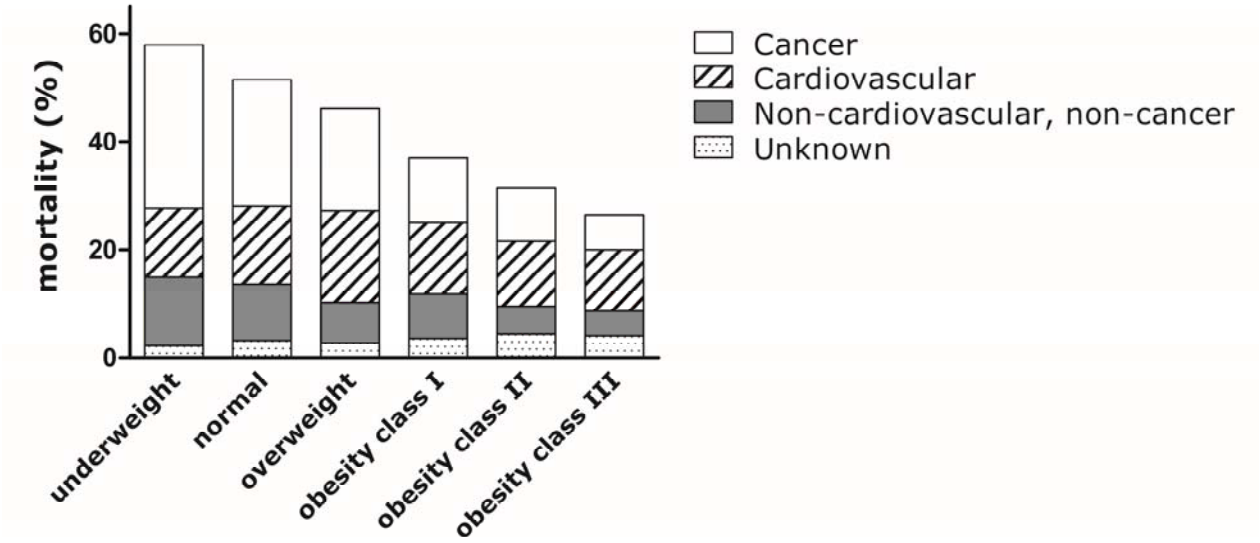


Fig. 4 Long-term and cause-specific mortality according to BMI categories



Tables

Table 1. Baseline characteristics of the study population

	Underweight (N=475)	Normal weight (N=4601)	Overweight (N=3500)	Obesity Class I (N=1311)	Obesity Class II (N= 368)	Obesity Class III (N=172)	P
Demographics							
Age (mean ± SD)	52 (± 19)	57 (± 16)	60 (± 15)	58 (±14)	56 (±14)	53 (±12)	< 0.001
Male (%)	52	62	65	49	30	20	< 0.001
Medical history (%)							
Ischemic heart disease	7	10	13	14	12	8	< 0.001
Cerebrovascular disease	3	6	7	7	7	4	0.005
Renal dysfunction	5	5	5	5	4	4	0.886
Heart failure	4	6	7	6	6	4	0.078
Diabetes Mellitus	30	36	41	45	48	49	< 0.001
Cancer	43	40	35	27	22	16	< 0.001
COPD	46	49	48	41	42	26	< 0.001
Smoker, current	53	40	32	29	26	29	< 0.001
Surgery risk (%)							< 0.001
Low	26	23	23	30	39	40	
Intermediate	65	64	61	59	54	56	
High	9	13	16	11	7	4	
Revised Cardiac Risk Index (%)							< 0.001
None	61	54	48	46	45	47	
1 risk factor	32	34	37	38	39	40	
2 risk factors	6	9	11	11	11	13	
≥ 3 risk factors	1	3	4	5	5	1	

Abbreviations: COPD chronic obstructive pulmonary disease; SD standard deviation

Table 2. Surgical procedures

	N	(%)
Low Cardiac Risk *	2596	25
Breast	132	1.3
Dental	54	0.5
Endocrine	121	1.2
Eye	623	6.0
Gynecology	579	5.6
Orthopedic	939	9.0
Reconstructive	148	1.4
Intermediate Cardiac Risk *	6461	62
Abdominal	2417	23.2
Carotid	26	0.2
Head and neck	1382	13.3
Neurologic	338	3.2
Pulmonary	814	7.8
Renal and urologic	1022	9.8
Other	462	4.4
High Cardiac Risk *	1370	13
Aortic	185	1.8
Peripheral vascular	294	2.8
Other vascular	891	8.5

** cardiac risk in non-cardiac surgery based on ESC guidelines [15]*

Table 3. Mortality rates and Hazard Ratios for mortality from all-cause, cerebro-cardiovascular and cancer

	Underweight	Normal weight	Overweight	Obesity Class I	Obesity Class II	Obesity Class III
all-cause mortality						
% unadjusted	58	52	46	37	31	27
HR	1.2	1.0	0.9	0.6	0.5	0.4
(95% CI)	1.0-1.3		0.8-0.9	0.6-0.7	0.4-0.6	0.3-0.6
adjusted HR*	1.4	1.0	0.8	0.7	0.7	0.7
(95% CI)	1.2-1.6		0.8-0.9	0.7-0.8	0.6-0.9	0.5-1.0
cerebro-cardiovascular mortality						
% unadjusted	13	15	18	14	13	12
HR	0.9	1.0	1.1	0.8	0.7	0.6
(95% CI)	0.6-1.1		1.0-1.2	0.7-1.0	0.5-0.9	0.4-1.0
adjusted HR*	1.2	1.0	0.9	0.8	1.0	1.3
(95% CI)	0.9-1.5		0.8-1.1	0.7-1.0	0.7-1.3	0.8-2.0
cancer mortality						
% unadjusted	31	24	19	12	10	7
HR	1.4	1.0	0.8	0.5	0.4	0.2
(95% CI)	1.1-1.6		0.7-0.8	0.4-0.6	0.3-0.5	0.1-0.4
adjusted HR*	1.4	1.0	0.8	0.7	0.7	0.5
(95% CI)	1.1-1.6		0.8-0.9	0.6-0.8	0.5-0.9	0.3-0.9

** adjusted for age, gender, RCRI, COPD and smoking status, surgery risk, cancer related surgery and year of surgery*

CHAPTER 4

The Influence of Polyvascular Disease on the Obesity Paradox in Vascular Surgery Patients

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The influence of polyvascular disease on the obesity paradox in vascular surgery patients

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Competition of interest: none.

Abstract

Background: Obesity is a risk factor for atherosclerosis, a polyvascular process associated with reduced survival. In nonvascular surgery populations, a paradox between body mass index (BMI) and survival is described. This paradox includes reduced survival in underweight patients, whereas overweight and obese patients have a survival benefit. No clear explanation for this paradox has been given. Therefore, we evaluated the presence of the obesity paradox in vascular surgery patients and the influence of polyvascular disease on the obesity paradox.

Methods: In this retrospective study, 2933 consecutive patients were classified according to their preoperative BMI (kg/m^2) and screened for polyvascular disease and cardiovascular risk factors before surgery. In addition, medication use at the time of discharge was noted. Outcome was all-cause mortality during a median follow-up of 6.0 years (interquartile range, 2-9 years).

Results: BMI (kg/m^2) groups included 68 (2.3%) underweight (BMI <18.5), 1379 (47.0%) normal (BMI 18.5-24.9, reference), 1175 (40.0%) overweight (BMI 25-29.9), and 311 (10.7%) obese (BMI >30) patients. No direct interaction between BMI, polyvascular disease, and long-term outcome was observed. Underweight was an independent predictor of mortality (hazard ratio, 1.65; 95% confidence interval, 1.22-2.22). In contrast, overweight protected for all-cause mortality (hazard ratio, 0.79; 95% confidence interval, 0.700-0.89). Cardioprotective medication usage in underweight patients was the lowest *(P* < .001), although treatment targets for risk factors were equally achieved within all treated groups.

Conclusion: Overweight patients referred for vascular surgery were characterized by an increased incidence of polyvascular disease and required more extensive medical treatment for cardiovascular risk factors at discharge. Long-term follow-up showed a paradox of reduced mortality in overweight patients.

INTRODUCTION

The prevalence of obesity among adults has been increasing in epidemic proportions and has become a critical problem in developed countries.[1] The American Heart Association and American College of Cardiology guidelines for secondary prevention in coronary artery disease (CAD) have listed obesity as a major modifiable cardiovascular risk factor.[2] Obesity has an important role in the atherosclerotic process because it promotes endothelial dysfunction, systemic inflammation, and a prothrombotic state.[3] More important, the process of atherosclerosis is often not limited to a single arterial location. The Reduction of Atherothrombosis for Continued Health registry showed that one of six patients with peripheral arterial disease (PAD), cerebrovascular disease, or CAD had involvement of one or two other arterial beds.[4] Moreover, the presence of polyvascular disease has been demonstrated as an independent predictor of long-term cardiovascular outcome in the general population.[5-7]

Although obesity is associated with an increased risk of developing cardiovascular disease in the general population, evidence from population-based studies with established atherosclerotic disease has indicated an obesity paradox, whereby obesity appears to be protective against an adverse prognosis.[8-10] No clear explanation for this discrepancy in survival rates between increased body mass index (BMI) and atherosclerotic disease has been found. Therefore, we performed the current study in a cohort of vascular surgery patients to evaluate (1) the prevalence of obesity and the association on long-term survival and (2) the association between polyvascular disease and medical treatment at time of discharge with respect to obesity, cardiovascular risk factor control, and long-term survival.

Methods

The study complies with the Declaration of Helsinki. Patient enrollment and approaching the municipal civil registries was performed after approval of the hospital's Ethics Committee.

Study design and population. This retrospective single-center study comprised a source population of 3612 consecutive major vascular operations, of which 254 (7%) were acute procedures and 3358 were elective (Fig 1). In the 3358 elective operations, 2933 unique patients were identified, and 425 repeated operations were performed in 311 (11%) of these 2933 patients. Patients who had more than one operation were included only once, based on their first

surgical procedure.[11] All patients underwent a major vascular surgical procedure between 1990 and 2008, which included open lower extremity revascularization, aneurysmatic abdominal aortic surgery, or carotid surgery. From 1990 until 2001, standard preoperative screening included a detailed cardiac history, physical examination, electrocardiogram, standard laboratory measurements, and additional stress testing if indicated. After 2002, standard preoperative echocardiography was added to the screening program.

Body mass index. Before surgery, body weight (kg) and length (m) were measured in all patients, and BMI was calculated (kg/m^2). The National Institutes of Health obesity classification[12] was used to divide the study population into the following four BMI categories (kg/m^2): underweight (BMI <18.5), normal weight (BMI 18.524.9), overweight (BMI 25-29.9), and obese (BMI >30).

Baseline characteristics. Medical records of every patient visit were reviewed by two authors (J.P.K. and W.J.F.) to determine the presence of documented CAD and cerebrovascular disease. CAD was defined as a documented history of ischemic heart disease (composite of angina pectoris, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting). The presence of coronary ischemia was established by one of the following techniques: exercise electrocardiogram, exercise testing with echocardiography, or computed tomography.[13] Patients with stable or unstable angina pectoris were classified as having documented CAD. Documented cerebrovascular disease was defined as a history of cerebrovascular accident or transient ischemic attack (confirmed by a computed tomography scan). Lower extremity arterial disease was defined as current intermittent claudication with ankle-brachial index <0.9 or a history of intermittent claudication with a previous intervention. Polyvascular disease was defined as the presence of more than one affected vascular beds.

Medication use and risk factors. The use of the following medication was recorded at discharge: aspirin, statins, β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and angiotensin-receptor blockers. According to the European Society of Cardiology guidelines, PAD patients have to be treated with aspirin (75-325 mg), statins (low- to intermediate-risk patients: target low-density lipoprotein-cholesterol [LDL-C] level <100 mg/dL, high-risk patients <70 mg/dL), and β-blockers in patients with ischemic heart disease, and those with a left ventricular ejection fraction <40% should receive ACE inhibitors.[14]

Risk factors determined at baseline included age, gender, smoking status, hypertension

(blood pressure >140/90 mm Hg in nondiabetics and >130/80 mm Hg in diabetics or requirement of antihypertensive medication), diabetes mellitus[15] (fasting blood glucose >7.0 mmol/L or requirement for insulin or oral antidiabetic medication), hypercholesterolemia (LDL-C >135 mg/dL or the requirement of lipid-lowering medication, or both), chronic heart failure, and chronic obstructive pulmonary disease (COPD), according to the Global Initiative on Obstructive Lung Diseases classification.[16] Control of cardiovascular risk factor was defined in line with the European Society of Cardiology guidelines,[14] including systolic blood pressure <140 mm Hg, diastolic blood pressure <90mmHg, LDL-C <100 mg/dL (2.5 mmol/L), glycemia <110 mg/dL (6.1 mmol/L), and smoking cessation >12 months. Good control was defined as three to five cardiovascular risk factors at target values and poor control was defined when zero to two cardiovascular risk factors were at targets.[6]

End points. The median follow-up of all patients was 6 years (interquartile range, 2-9 years). The primary study end point was the occurrence of all-cause mortality. Survival was assessed by querying the municipal civil registries. Cause of death was ascertained by examining death certificates or by reviewing medical records.

Statistical analyses. Dichotomous data are described as numbers and percentages. Continuous variables are described as means ± standard deviation. Continuous data were compared using analysis of variance, and categoric data were compared using a χ^2 test. Cumulative survival of the BMI groups was determined by the Kaplan-Meier method and compared using the log-rank test. Cox regression models were used to investigate the association between BMI groups (patients with normal BMI as reference group) and death during long-term follow-up. Censoring for the 311 patients with repeated surgery was performed at the second surgical procedure.

All multivariate analyses were primarily adjusted for demographics (age and gender), cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, and COPD), site of surgery (lower extremity, abdominal aortic, or carotid), year of surgery, repeated surgery during follow-up, history of malignancy, and medication use as recommended in PAD patients, including aspirin, statins, and β-blockers, in case of prior myocardial infarction, and ACE inhibitors in patients with heart failure.[4] To evaluate the effect of discharge use of aspirin, statins, p-blockers, and ACE inhibitors on long-term outcome, multivariate Cox regression analyses were performed with propensity score adjustment for each medication. Separate propensity scores were developed with logistic regression analyses for each type of medication.

Variables included in the propensity score were demographics (age and gender), cardiovascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia, chronic heart failure, and COPD), site of surgery (lower extremity, abdominal aortic or carotid), year of surgery, repeated surgery during follow-up, and a history of malignancy. To study the influence of polyvascular disease on the BMI groups, we used interactions terms between BMI and polyvascular disease. Statistical analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, Ill). These models were used to calculate hazard ratios (HRs), along with their 95% confidence intervals (CIs). A value of $P < .05$ (two-sided) was considered statistically significant.

RESULTS

Description of the study population. The final study population consisted of 2933 patients referred for elective major vascular surgery (Fig 1). Abdominal aortic surgery was performed in 1170 (40%), lower extremity revascularization in 1031 (35%), and carotid surgery in 732 patients (25%). At baseline, the 2933 patients were categorized into preoperative BMI groups and included 68 underweight (2.3%), 1379 normal-weight (47.0%; reference group), 1175 overweight (40.0%), and 311 obese patients (10.7%; Table I). A positive history of malignancies was less often observed in patients who were overweight (188 of 1175 [16%]) or obese (44 of 311 [14%]). The distribution of the surgical procedures is described in Fig 2. Patients with normal weight most often had lower extremity revascularization compared with the other groups (P < .01). In the total study population, coronary artery disease was detected in 1248 patients (43%) and cerebrovascular disease in 1037 patients (35%).

Short-term and long-term outcome. Of the 2933 patients, 112 died during the first 30 postoperative days, for a mortality rate of 4.0%. Mortality rates by BMI group were underweight, 4% (3 of 68); normal-weight, 7% (97 of 1379); overweight, 3% (35 of 1175); and obese, 5% (16 of 311). The difference in the mortality rates between these groups was not statistically significant (P=0.125). During long-term follow-up, there were 1389 deaths (47%; Table II). Mortality was 69% in underweight patients (49 of 68) compared with 52% in normal-weight patients (717 of 1379), which was significant (P<0.001). In contrast, overweight and obese patients had significantly lower mortality rates of43% (507 of 1175) and 38% (118 of 311, P<0.001), respectively. A non-cardiovascular cause of death occurred in 434 of 1389 patients (31%), of which 258 (59%) were cancer-related. Patients in the underweight group demonstrated a 44% rate (30 of 68) of cancer-related death compared with 23% for the normal-weight (317 of 1379),

22% for the overweight (259 in 1175), and 18% for the obesity group (56 of 311), which was statistically significant (P<0.01). Univariate Kaplan-Meier curves for mortality, stratified according the BMI groups, demonstrated that underweight patients had lower survival rates than patients with a normal BMI (Fig 3). In contrast, overweight or obese patients had higher survival rates than patients with a normal BMI. A log-rank test was used to compare cumulative survival between underweight vs normal (P=0.002), overweight vs. normal (P< 0.001) and obesity vs. normal (P=0.01).

After multivariate regression analyses, patients within the lowest BMI group had an increased risk for mortality (HR=2.10; 95% CI=1.45-3.03) compared with patients within the normal-weight BMI (Table III). In contrast, overweight patients had a reduced risk for mortality (HR=0.77; 95% CI=0.69-0.86). Other independent predictors for mortality were age (HR=1.05; 95% CI=1.04-1.06), COPD (HR=1.30; 95% CI=1.14-1.48), diabetes mellitus (HR=1.25; 95% CI=1.08-1.45), and chronic heart failure (HR=1.47; 95% CI=1.21-1.79).

Polyvascular disease and outcome. Polyvascular disease was present in 28 of 68 underweight (41%), in 703 of 1379 normal-weight (51%), and in 817 of 1486 overweight and obese patients (55%; P=0.02). When interaction terms were used to identify the direct influence of polyvascular disease on the relations between BMI and survival rates, no direct interaction was observed between the different BMI groups and polyvascular disease for long-term survival. In additional subgroup analyses, patients were subdivided into two groups with either BMI <25 kg/m^2 or BMI >25 kg/m^2. In both groups, the presence of polyvascular disease was associated with reduced long-term survival rates. Kaplan-Meier long-term survival estimates are demonstrated in Fig 4. In both groups, the presence of multiply affected vascular beds was associated with an increased mortality risk during long-term follow-up. In multivariate analyses, patients with BMI <25 kg/m^2 or BMI >25 kg/m^2 and concomitant polyvascular disease had an independent increased mortality risk (HR=1.22; 95% CI=1.051.42 and HR=1.33; 95% CI=1.13-1.58; respectively) compared with patients without polyvascular disease.

Medication use and risk factor control. Medication use at discharge demonstrated an under-treatment of underweight patients compared with overweight or obese patients. The standard cardioprotective medical treatment for PAD patients included aspirin, statins, β-blockers, and ACE inhibitors. Fig 5 provides an overview of the number of drugs per BMI category and shows that 34 of 68 (50%) of the underweight patients received no medical treatment at discharge. A

significant trend for more use of these four types of drugs was observed in patients with higher BMI compared with patients with lower BMI (P<0.001). During the follow-up period, aspirin (HR=0.71; 95% CI=0.63-0.80) and statins (HR=0.69; 95% CI=0.59-0.80) were significantly associated with lower mortality rates in propensity-adjusted analyses.

The atherosclerotic risk factors of hypertension, diabetes mellitus, and dyslipidemia were related to higher BMI because the prevalence in patients with obesity was significantly higher (P<0.001) compared with lower BMI. Mean preoperative systolic and diastolic blood pressure for the total were 148±48 and 82±25 mm Hg, and no significant differences between the BMI groups were observed (P=0.55).

Preoperative mean high-density lipoprotein-cholesterol (HDL-C) was highest in the underweight group (53.0 ± 19 mg/dL [1.37 ± 0.50 mmol/L]) and lowest in the obesity groups (43±13 mg/dL [1.10±0.34 mmol/L]; P<0.001). Mean LDL-C of the total population was 123±48 mg/dL (3.19±1.24 mmol/L), and no significant differences in mean preoperative LDL-C were observed among the BMI groups.

Several important differences between gender, smoking habits, and the BMI groups were observed. Of the 30 underweight women, 15 (50%) were current smokers compared with 32 of the 101 obese women (32%). In addition, only 1 underweight woman (3%) stopped smoking compared with 136 of 714 women (19%) in the other BMI groups. In the men, the number of previous smokers showed a clear association with the increase in BMI: 8 of 38 (21%) of the underweight men and 65 of 210 (31%) of the obese men were previous smokers. The number of current smokers decreased from 17 of 38 (45%) in underweight men to 67 of 210 (32%) in obese men. Finally, in all patients, current smoking was not an independent predictor of increased mortality risk; however, those patients who stopped smoking had a significantly lower mortality risk (HR,=0.84; 95% CI=0.72-0.98) compared with those who continued smoking. There were no differences between the BMI groups regarding the number of controlled cardiovascular risk factors. Good control (3 to 5 risk factors controlled) was achieved in 53% (36 of 68) of the underweight group compared with 54% (745 of 1379) of the normal-weight, 53% (623 of 1175) of the overweight, and 55% (171 of 311) of the obesity group (P=0.88). In separate analyses for individual risk factors, significant differences were only detected for target LDL-C <100 mg/dL (2.5 mmol/L). Underweight patients had the lowest effect rate of statin therapy, as only 6 of 68 (9%) received the target compared with 179 of 1379 (13%) normal-weight, 188 of 1175 (16%)

overweight, and 62 of 311 (20%) obese patients (P =0.005).

DISCUSSION

The current study demonstrated that overweight patients had a reduced long-term mortality risk. We observed a low prevalence of polyvascular disease in patients with low BMI compared with a significantly higher prevalence in patients with BMI >25 kg/m^2. The increased prevalence of polyvascular disease in overweight and obese patients was independently associated with an increased mortality risk; however, no direct interaction between BMI and polyvascular disease was observed. Medical treatment at time of discharge in overweight and obese patients was highest, because only 18% of these patients received no treatment. Remarkably, risk factor control was achieved equally in all treated BMI groups.

In the pathogenesis and complications of obesity, the adipocyte has a substantial role acting as an endocrine organ.[17] Food intake and energy metabolism is controlled by the hormone leptin, which is derived from adipocytes. Increased leptin levels have been related to the development of cardiovascular disease.[18] On the one hand, obesity stimulates the development of leptin resistance, which in turn influences insulin resistance and eventually results in type-II diabetes mellitus. On the other hand, obesity promotes hyperleptinemia, which stimulates increasing blood pressure through adverse effects on the vascular wall.[18] Several studies, however, have not been able to demonstrate a clear role for leptin.

Other more recent studies have demonstrated the involvement of other adipokines and the immune system through low-grade inflammation of adipose tissue, reflected by C-reactive protein elevations.[19,20] These pathophysiologic mechanisms are important in the atherosclerotic process, a systematic inflammatory disease with clinical presentations in multiple vascular beds. Obesity has been identified as an important risk factor for developing CAD; however, once this has been established, the correlation between obesity and mortality is paradoxic. Therefore, other factors, such as the presence of polyvascular disease or medical undertreatment, could be involved in the obesity paradox on long-term outcome.

The obesity paradox has extensively been described in patient cohorts with established CAD. A meta-analysis by Romero-Corral and colleagues summarized these studies and demonstrated that patients with overweight and mild obesity had lower mortality rates than normal-weight patients.[10] In contrast, patients who were underweight had an increased all-cause and

cardiovascular mortality risk compared with normal-weight patients.[10] The obesity paradox was also recently demonstrated in a cohort of almost 5000 patients undergoing percutaneous coronary intervention.[8] Mullen et al[21] demonstrated that overweight and moderately obese patients in the general surgery population have paradoxically lower crude and adjusted risks of mortality compared with normal-weight patients. Galal et al[22] have shown an excess mortality rate among underweight patients with PAD, which was largely explained by the over-representation of individuals with moderate-to-severe COPD.

Our study results are in line with these studies regarding the paradoxically increased mortality rates in underweight patients during long-term follow-up. Short-term postoperative outcome was not associated with an increased mortality risk for one of the BMI groups compared with normal weight. The survival curves suggest an increased mortality risk for the underweight patients; however, this is very likely a result of the small number of patients in this group.

Gulsvik et al[23] demonstrated a U-shaped risk curve for total mortality in the elderly, which was confirmed by our results in high-risk vascular surgery patients. Furthermore, overweight was associated with a survival benefit compared with normal weight; however, obesity showed no relation with an increased or decreased mortality risk. In the present study, we used the National Institutes of Health obesity classification[12] to study the associations with the obesity paradox. It could be argued that cohort should be defined into four equal BMI quartiles because this could have more statistical significance. However, the main purpose of the present study was to provide the clinician with a practical and easy applicable definition; therefore, we used the predefined BMI groups.

More important, although several possible explanations for the obesity paradox have been suggested, the influence of polyvascular disease has not been investigated. We demonstrated that overweight and obese patients had a significant increased incidence of polyvascular disease compared with a low incidence in underweight patients. Remarkably, patients with BMI <25 kg/m^2 or BMI >25 kg/m^2 and concomitant polyvascular disease had an increased mortality risk compared with those without polyvascular disease. Because no direct interaction between BMI, polyvascular disease and long-term mortality was observed, it cannot be concluded that polyvascular disease is an explanation for the obesity paradox.

In the present study, patients with low BMI received less frequent medical treatment at

discharge compared with overweight or obese patients. Results from the Get With The Guidelines Database in CAD patients showed that higher BMI was associated with increased use of standard medical therapies such as aspirin, β-blockers, ACE inhibitors, and lipid-lowering therapies.[24] This relation between BMI and treatment rates may represent the response of physicians to a more visible risk factor compared with the less visible traditional risk factors such as hypertension and diabetes. However, because obese patients had an increased incidence of polyvascular disease, this could also be the reason for intensified treatment.

In the present study, the low and normal BMI groups were consistently associated with a lower prevalence of established cardiovascular risk factors, with the exception of current smoking. Therefore, these BMI groups were less likely to receive effective secondary prevention therapies such as lifestyle interventions and medical treatment. In contrast, overweight and obese patients received more aggressive medical treatment. Because overweight and obese patients are younger at first presentation, a more aggressive treatment strategy may be performed.

The importance of socioeconomic status and dietary habits also needs to be acknowledged. These are known risk factors for developing overweight and have been associated with adverse long-term outcomes.[25,26] Although overweight seems to have a protective perioperative effect, and overweight patients are more likely to receive earlier and extended medical attention, they remain at increased risk for developing metabolic and cardiac complications due to their increased body weight.

Even though low BMI patients received less intensive medical treatment at the time of hospitalization, risk factor control intensity in those patients who did receive treatment was comparable with the other BMI groups. Of note, statin therapy was an independent predictor for increased survival rates; however, LDL-C lowering could be less efficient in patients with low body weight. Our results emphasize the importance of risk factor stratification and modification in vascular surgery patients with a low BMI, while adequate medical treatment at discharge was associated with improved survival rates in all groups of patients.

Potential limitations of the current study merit consideration. First, this study has the disadvantage of a retrospective design and included a patient population of vascular surgery referrals that might not be fully representative for the general population.

Second, although suggested by the survival curves, short-term postoperative mortality (30 days) was not significantly different among the BMI groups. This is very likely a result of the small number of patients in the underweight group, and these results need to be interpreted with some caution.

Third, the results of this study showing significant associations between medical treatment at discharge and increased survival rates need to be interpreted with some caution because no evaluation of treatment adherence during follow-up was available.

Fourth, because AAA development is not causally related to the presence of atherosclerotic disease, although there are many common risk factors, appropriate medical therapy could be underestimated in these patients.

Finally, data on socioeconomic status and dietary habits were not available, and therefore, we cannot rule out the possibility of confounding by these factors. In addition, although we adjusted the multivariate analyses for possible confounders (smoking, cancer, medical treatment) of the primary end point, we cannot rule out the possibility of residual confounding.

CONCLUSIONS

In this population of vascular surgery patients, more than half were categorized as overweight or obese. The prevalence of polyvascular disease was significantly higher in patients who were overweight or obese. The high prevalence of polyvascular disease in overweight and obese patients was independently associated with increased mortality compared with patients with monovascular disease; however, no direct interaction between polyvascular disease and BMI was observed. A significant trend for less medical treatment at discharge in relation to decreasing BMI was observed. Underweight patients were at an increased long-term mortality risk, whereas overweight patients had a reduced mortality risk compared with normal-weight patients.

Tables and Figures:

Table I. Baseline characteristics of the study population

Variables	Underweight (n = 68)	Normal (reference) (n = 1379)	Overweight (n = 1175)	Obese (n = 311)	P
Demographics					
Age, mean ± SD years	66 ± 12	67 ± 12	67 ± 10	64 ± 11	<.001
Male, No. (%)	38(56)	1040 (75)	901 (77)	210 (68)	<.001
History, No. (%)					
Malignancies	33 (49)	359(26)	188(16%)	44 (14)	<.001
CVA/TIA	11 (16)	469(34)	447 (38)	110 (35)	<.001
Lower extremity PAD	24 (35)	389(28)	257 (22)	96 (31)	<.001
Aortic aneurysmatic disease	3(4)	34(3)	25 (2)	5 (2)	.50
Ischemic heart disease	22 (32)	557 (40)	535 (46)	134 (43)	.02
Cardiovascular risk factors, No. (%)					
Smoking					.02
No	27 (40)	522 (38)	462 (39)	128 (41)	
Current	32 (47)	546 (40)	415 (35)	99 (32)	
History	9(13)	311 (23)	298 (25)	84 (27)	
Hypertension	21 (31)	665 (48)	646 (50)	182 (59)	<.001
Diabetes mellitus	8 (12)	178 (13)	208 (18)	97 (31)	<.001
Dyslipidemia	10 (15)	347 (25)	334 (28)	107 (24)	<.001
Chronic heart failure	3(4)	102 (7)	83 (7)	18 (6)	.63
COPD	8 (12)	273 (20)	219 (19)	57(18)	.38
Medication at discharge, No. (%)					
Aspirin	17(25)	670 (49)	621 (53)	194(62)	<.001
Statin	15 (22)	454 (33)	501 (43)	161 (52)	<.001
p-blocking agents	20 (29)	575 (42)	529 (45)	169(54)	<.001
Diuretics	11 (16)	285 (21)	293 (25)	107(34)	<.001
ACE inhibitors	9(13)	330 (24)	300 (26)	101 (35)	.002
Calcium antagonists	15 (22)	317 (23)	300 (26)	79 (25)	.45
Angiotensin receptor blockers	2(3)	49 (4)	77 (7)	29 (9)	<.001

ACE, Angiotensin-converting enzyme; *COPD,* chronic obstructive pulmonary disease; *CVA/TIA,* cerebrovascular accident/transient ischemic attack.

Table II. Primary cause of death of the study population

Primary cause of death	*Patients No. (%)*
Cardiac arrhythmia, unspecified	27 (2)
Heart failure	122(9)
Stroke	66 (5)
Hypovolemic shock	48(3)
Acute myocardial infarction	180(13)
Cardiovascular disease, unspecified	335(24)
Septicemia	36 (3)
Cancer[a]	260(19)
Complications of surgical and medical care not elsewhere classified[b]	29 (2)
Chronic obstructive lung disease[c]	85 (6)
Pneumonia and influenza[d]	22(1)
Symptoms, signs, and abnormal clinical or lab findings, not elsewhere classified	73 (5)
Ill-defined and unknown causes ofmortality	106 (8)
Total	1389 (100)

Of these groups, 35,[a] 14,[b] 12,[c] and 10[d] were classified as a secondary cause of death due to secondary cardiac complications.

Table III. Long-term survival of all patients

Events	*No. (%)*	*Univariate HR (95% CI)*	*Multivariate[a] HR (95% CI)*
All-cause mortality			
Underweight	49/68 (72)	1.60 (1.19-2.15)	2.10 (1.45-3.03)
Normal	717/1379 (51.9)	Reference	Reference
Overweight	507/1175 (43.1)	0.76 (0.68-0.86)	0.77 (0.69-0.86)
Obesity	118/311 (37.9)	0.78 (0.64-0.95)	0.93 (0.76-1.13)

CI, Confidence interval; *HR,* hazard ratio.

[a]Adjustment for age, gender, polyvascular disease, smoking, hypertension, diabetes mellitus, hypercholesterolemia, heart failure, chronic obstructive pulmonary disease, site of surgery, year of surgery, aspirin, statins, and ^-blockers.

Fig 1. Flow diagram shows the source and final study population

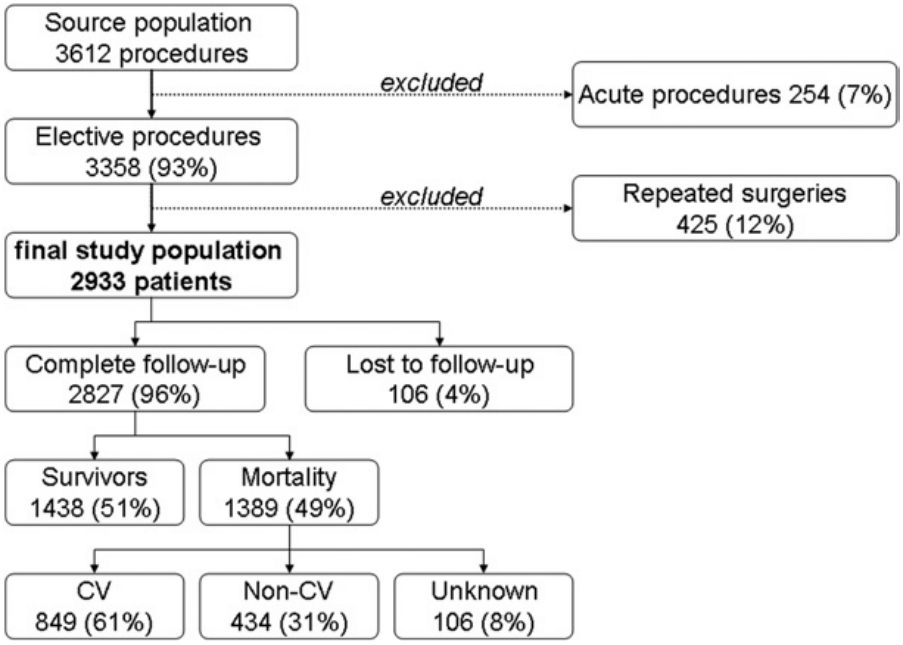


Fig 2. Distribution of the sites of the surgical procedures are shown for the body mass index groups, including lower extremity revascularization, abdominal aortic surgery, and carotid surgery.

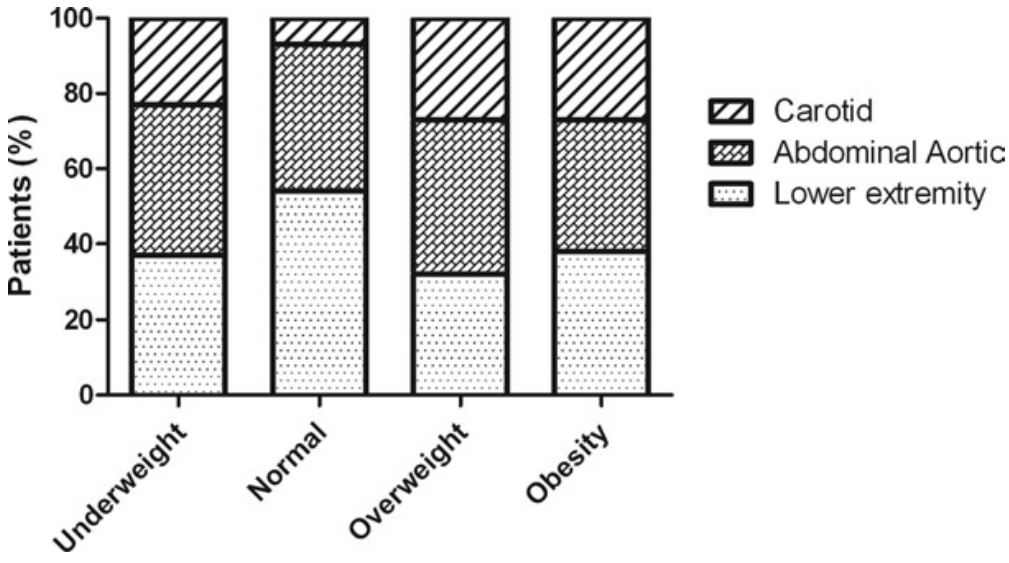
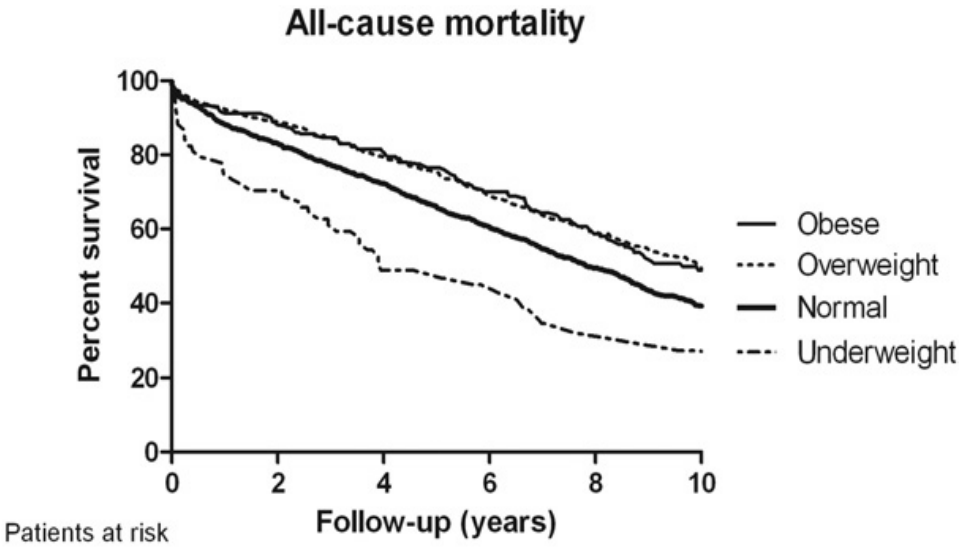


Fig 3. Cumulative survival is shown by Kaplan-Meier analysis of the risk of all-cause mortality stratified according the four body mass index groups.



Patients at risk						
Obese	311	206	165	128	88	49
Overweight	1175	896	697	543	410	266
Normal	1379	982	763	587	429	262
Underweight	68	47	27	22	13	10

Fig 4. Kaplan-Meier estimates show cumulative survival stratified according to the presence of monovascular or polyvascular disease in patients with a **(left)** body mass index <25 kg/m^2 or **(right)** >25 kg/m^2

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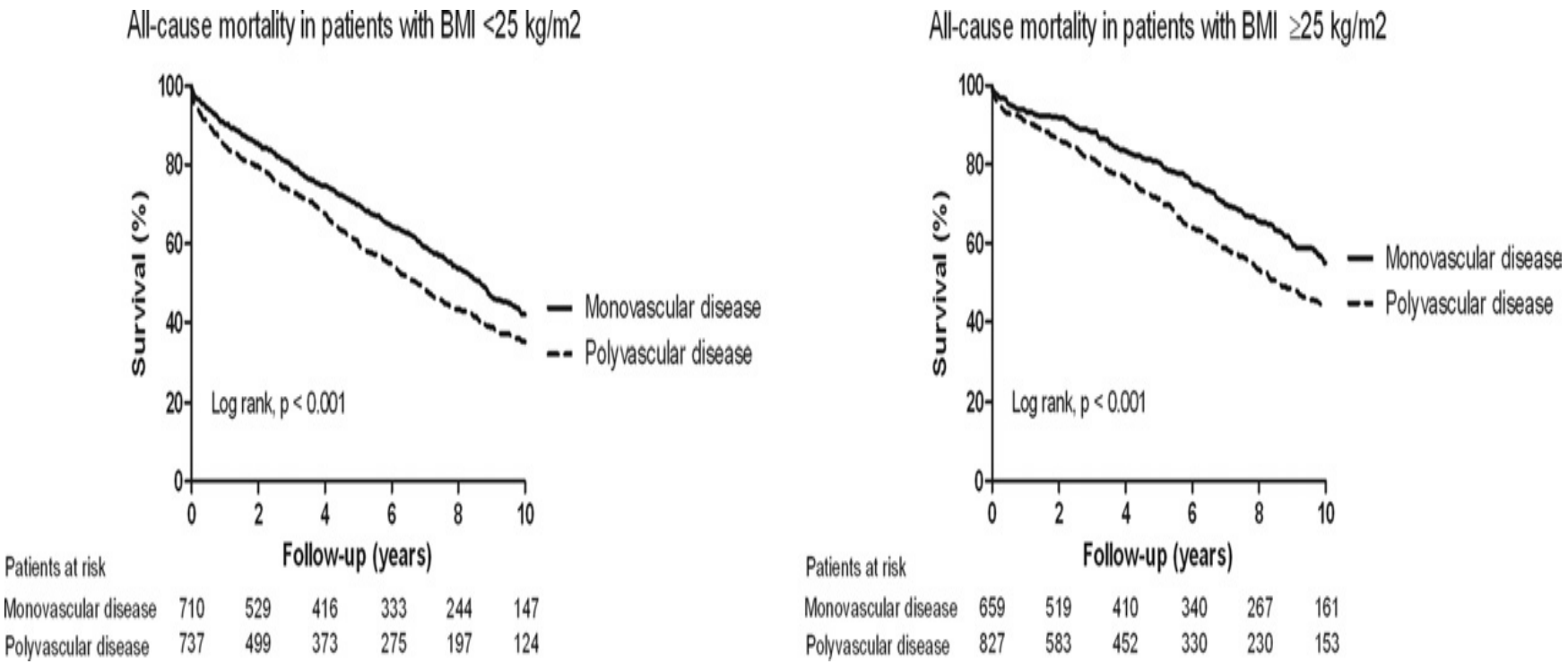
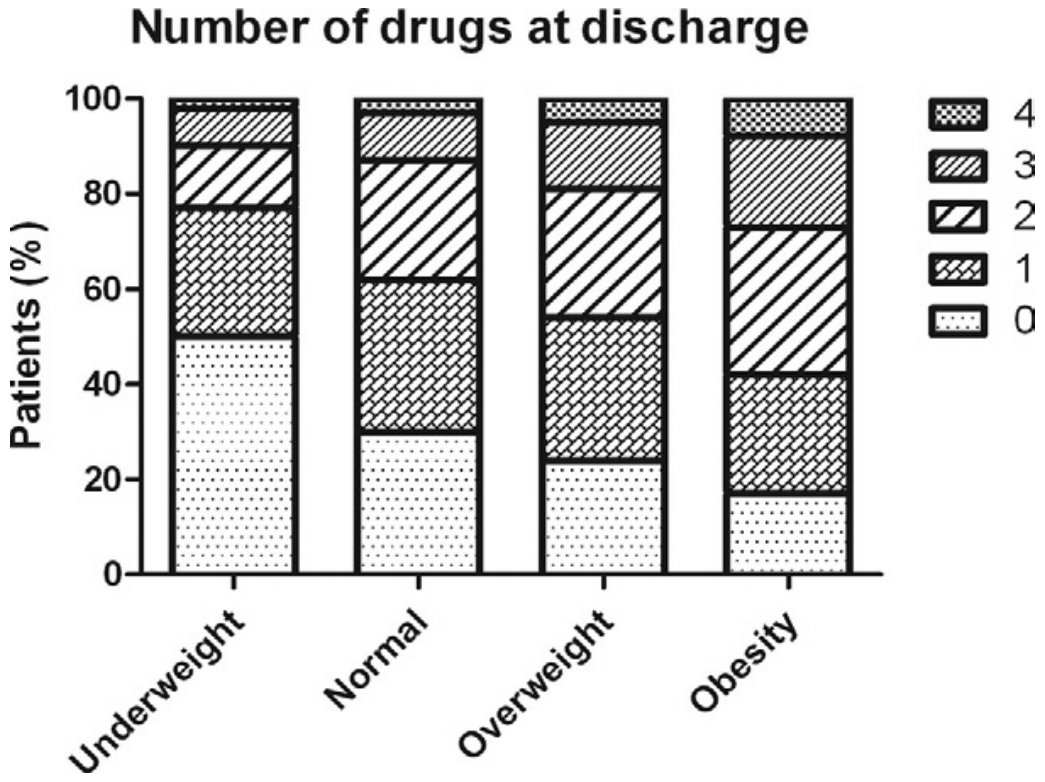


Fig 5. Number of drugs used at the time of discharge for each body mass index group, including aspirin, statin, β-blockers, and angiotensin-converting enzyme inhibitors.



REFERENCES

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 19992004. JAMA 2006;295:1549-55.

2. Smith SC Jr, Blair SN, Bonow RO, Brass LM, Cerqueira MD, Dracup K, et al. AHA/ACC Guidelines for Preventing Heart Attack and Death in Patients With Atherosclerotic Cardiovascular Disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. J Am Coll Cardiol 2001;38:1581-3.

3. Lavie CJ, Milani RV. Obesity and cardiovascular disease: the Hippocrates paradox? J Am Coll Cardiol 2003;42:677-9.

4. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295: 180-9.

5. Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. Eur Heart J 2009;30:1195-202.

6. Cacoub PP, Abola MT, Baumgartner I, Bhatt DL, Creager MA, Liau CS, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Atherosclerosis 2009;204:e86-92.

7. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317-24.

8. Hastie CE, Padmanabhan S, Slack R, PellAC, Oldroyd KG, Flapan AD, et al. Obesity paradox

in a cohort of4880 consecutive patients under- goingpercutaneouscoronaryintervention. EurHeartJ2010;31:222-6.

9. McGee DL. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. Ann Epidemiol 2005;15:87-97.

10. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666-78.

11. van Kuijk JP, Flu WJ, Welten GM, Hoeks SE, Chonchol M, Vidakovic R, et al. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. Eur Heart J 2010; 31:992-9.

12. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Am J Clin Nutr 1998;68:899-917.

13. O'Rourke RA, Brundage BH, FroelicherVF, Greenland P, GrundySM, Hachamovitch R, et al. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. J Am Coll Cardiol 2000;36:326-40.

14. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur Heart J 2009;30(22):2769-812.

15. Diagnosis and classification of diabetes mellitus. Diabetes Care 2009; 32(Suppl 1):S62-67.

16. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-55.

17. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898-918.

18. Martin SS, QasimA, ReillyMP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. J Am Coll Cardiol 2008;52:1201-10.

19. Enriori PJ, Evans AE, Sinnayah P, Cowley MA. Leptin resistance and obesity. Obesity (Silver Spring) 2006;14(suppl 5):254-8S.

20. Romero-Corral A, Sierra-Johnson J, Lopez-Jimenez F, Thomas RJ, Singh P, Hoffmann M, et al. Relationships between leptin and C- reactive protein with cardiovascular disease in the adult general population. Nat Clin Pract Cardiovasc Med 2008;5:418-25.

21. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. Ann Surg 2009;250:166-72.

22. Galal W, van Gestel YR, Hoeks SE, Sin DD, Winkel TA, Bax JJ, et al. The obesity paradox in patients with peripheral arterial disease. Chest 2008;134:925-30.

23. GulsvikAK,Thelle DS, Mowe M,WyllerTB. Increasedmortalityin the slim elderly: a 42 years follow-up study in a general population. Eur J Epidemiol. 2009;24:683-90.

24. Steinberg BA, Cannon CP, Hernandez AF, Pan W, Peterson ED, Fonarow GC. Medical therapies and invasive treatments for coronary artery disease by body mass: the “obesity paradox” in the Get With The Guidelines database. Am J Cardiol 2007;100:1331-5.

25. Burke GL, Arnold AM, Bild DE, Cushman M, Fried LP, Newman A, et al. Factors associated with healthy aging: the cardiovascular health study. J Am Geriatr Soc 2001;49:254-62.

26. Gregory IN. Comparisons between geographies of mortality and deprivation from the 1900s and 2001: spatial analysis ofcensus and mortality statistics. BMJ 2009;339:b3454.

CHAPTER 5

The Obesity Paradox in the Surgical population

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The Obesity Paradox in the Surgical Population

Abstract

Background: Despite the medical hazards of obesity, recent reports examining body mass index (BMI) show an inverse relationship with morbidity and mortality in the surgical patient. This phenomenon is known as the 'obesity paradox'. The aim of this review is to summarize both the literature concerned with the obesity paradox in the surgical setting, as well as the theories explaining its causation.

Methods: PubMed was searched to identify available literature. Search criteria included obesity paradox and BMI paradox, and studies in which BMI was used as a measure of body fat were potentially eligible for inclusion in this review.

Results: The obesity paradox has been demonstrated in cardiac and in non-cardiac surgery patients. Underweight and morbidly obese patients displayed the worse outcomes, both postoperatively as well as at long-term follow-up. Hypotheses to explain the obesity paradox include increased lean body mass, (protective) peripheral body fat, reduced inflammatory response, genetics and a decline in cardiovascular disease risk factors, but probably unknown factors contribute too.

Conclusions: Patients at the extremes of BMI, both the underweight and the morbid obese, seem to have the highest postoperative morbidity and

mortality hazard, which even persists at long-term. The cause of the obesity paradox is probably multi-factorial. This offers potential for future research in order to improve outcomes for persons on both sides of the ‘optimum BMI’.

Introduction

With advancement of medical care in modern societies, two distinct growing phenomena are observed, which pose new challenges to the surgeon. These are the overweight and obesity epidemic on the one hand, and the growing elderly population on the other hand.[1-3] These two categories of patients share a number of risk factors and associated comorbidities that predispose them to cardiovascular and other life-threatening complications.[4,5]

Body mass index (BMI), formerly known as Quetelet's index, has been introduced to public health science as a proxy of overall body fat content. It is calculated by dividing weight in kilograms by the square of height in meters. In late and even in upcoming years, much attention has been paid to this index and to other measures of total or abdominal fat, due to the increasing prevalence of overweight and obesity. Because of its simplicity, BMI has gained widespread acceptance and application in daily clinical practice. The World Health Organization (WHO) has defined different BMI categories (Table 1).[6,7]

Clinical research in the surgical population frequently focused on the prognostic value of certain clinical variables obtained from the preoperative assessment and the perioperative course.[8-11] Some of these variables are incorporated in guidelines regarding preoperative cardiovascular management in non-cardiac surgery,[12] which have been shown to reduce

postoperative cardiac events and improve long-term outcomes. Furthermore, recognition and optimization of other, non-cardiac, chronic ailment conditions prior to surgery can also be beneficial, both in the perioperative stage as well as for the long-term.[13] Although several preoperative risk-scoring systems exist,[14] BMI has not been included, since it was not considered as an independent (preoperative) risk factor or predictor for postoperative and long-term outcomes.

The purpose of this article is to give an overview of the relationship between BMI and outcome in the surgical population, reporting both postoperative and long-term outcomes. Furthermore, the literature regarding the inverse relationship between BMI and outcome, known as the obesity paradox, as well as the theories explaining its causation, are reviewed.

Methods

We performed a PubMed search to identify available literature up to January 1st, 2012. Search criteria included obesity paradox and BMI paradox, each of which was subsequently combined with additional search criteria including surgery, general surgery, cardiac surgery, outcome, and survival to narrow search results. Search criteria were restricted to English language, humans, and adults (age > 19 years). Original articles (observational, cohort, case-

control, cross-sectional, longitudinal and experimental), systematic reviews and meta-analyses were considered for inclusion in the review. Eligible studies were first identified by title, and abstracts in which BMI was used as a measure of body fat were retrieved as full-text papers. Additional studies were identified after reviewing related PubMed citations and references of the included papers.

The risks of obesity in the surgical patient

The worldwide broadening of the obesity epidemic has also affected surgery, not only because more surgical patients are obese, but also because of an increase in obesity related diseases that require surgery.[1,4] Substantial data from literature showed the preponderance of cardiovascular risk factors in the overweight and obese population.[1,4,15] Moreover, increased body mass was found to be a predictor of increased cardiac risk, independent of cardiovascular risk factors.[16] Obesity is also known to be related to left-ventricular morphological changes and impaired diastolic function.[17] Therefore, the observation of a strong association between obesity and long-term mortality in several studies was not unexpected.[18,19]

However, the perioperative risks associated with obesity might have been overestimated. Increased anesthetic and surgical interest in obesity,

particularly in bariatric surgery, might have led to better care of obese patients and lower perioperative complication rates.[20,21] Several prospective cohort studies with strict definitions of postoperative morbidity, demonstrated that in general (non-bariatric) surgery, postoperative complications like surgical site infections are related to obesity,[22-27] with the highest rates in morbid (class III) obese patients.[22,24,26,27] In addition, morbidly obese patients had the highest postoperative mortality rates.[23,24,26,27] On the other hand, the lowest postoperative mortality risk was reported in the overweight and obese class I and class II patients.[23,24,27] In several surgical oncology populations the postoperative mortality rates did not differ between normal weight and overweight and obese patients.[25,28-30] However, most data regarding the risks of obesity in the (non-bariatric) surgical population are obtained from large-scale studies in cardiac surgery patients. Since overweight and obesity are known to promote the progression of coronary heart disease,[7] it is not surprising that around two thirds of all coronary artery bypass grafting (CABG) surgery is performed in overweight and obese patients.[31,32] Similar to non-cardiac surgery, several prospective studies in CABG surgery demonstrated that obesity was shown to be related to postoperative morbidity, with the highest rates of deep sternal wound infection and prolonged ventilation and hospitalization in moderate (class II) and morbid (class III) obese patients.[33-35] However, the majority of cardiac surgery studies, including

CABG studies, did not report adverse associations with postoperative morbidity[31,32,36] or mortality in obese patients.[31,32,35-38] It is important to notice that current studies in various surgical populations do not make a distinction between obese surgical patients with normal metabolic profiles and those with diabetes, although it is widely known that diabetes adversely affects postoperative outcomes.

Despite the large body of evidence showing that postoperative mortality is not increased in the majority of obese patients undergoing surgery, much attention has been paid to the association with postoperative morbidity, which might have led to a negative attitude towards obesity as a co-morbid condition in patients requiring surgery.

The obesity paradox

Recent epidemiological studies in the general population have shown a longer life expectancy in modern societies with prevalent overweight and obesity, compared to those that did not join the obesity epidemic.[39,40] The inverse relationship between body fat composition, particularly defined by the BMI, and all-cause mortality, is frequently referred to as the *obesity paradox*. The more comprehensive term *reverse epidemiology* also comprises the obesity paradox. It represents the unexplained

counterintuitive relationship of traditional cardiovascular risk factors and mortality in various (patient) populations.[41-44]

Many studies in surgical populations have demonstrated a similar paradoxical relationship between BMI and postoperative mortality, with the highest postoperative mortality risks in the underweight and morbid (class III) obese patients (Figure 1). The obesity paradox has been shown in various surgical populations, both in cardiac[31,32,34,36-38] and in non-cardiac surgery.[23,24,26,27]

The majority of studies examining the effects of BMI on surgical outcome merely studied short-term (i.e. postoperative) mortality; however some also reported long-term survival.[25,29,30,33,37,45-48] Underweight patients displayed the worse long-term survival, both in non-cardiac[45] and in cardiac surgery.[33,46,48] Overweight and obese patients showed conflicting results regarding long-term survival. Studies in vascular surgery,[45] oncology surgery[29,30] and cardiac surgery[37] reported survival benefit for overweight and obese patients, whereas other studies in oncology surgery[25] and cardiac surgery[47] did not demonstrate any association with long-term survival.

Table 2 gives an overview of different patient populations in which an inverse relationship between BMI and mortality was demonstrated. Most of these studies were conducted in Western populations; however, the obesity paradox has recently been described in East Asians as well.[59]

The paradox theories

Since the first observation of the obesity paradox, several suggestions were made to overcome the unexpected survival benefit of the overweight and obese. One suggestion was that the values of BMI cut-offs representing the categories defined by the WHO should be revised, so that overweight patients showing survival improvement should merge into the control group i.e. the normal BMI population.[60] However, it is important to consider that BMI does not discriminate between fat mass and lean mass, and as a result, BMI does not adequately reflect adiposity.[61,62] Therefore, it might be that overweight and (mild) obese persons do not have more fat, but instead have a preserved or increased lean body mass, which would offer a possible explanation for the survival benefit in these groups. Consequently, it has been suggested to omit the BMI completely as an index of body fat and replace it with more accurate indices such as waist circumference, waist-to-hip ratio and waist-to-height ratio, and with computed tomographic measurement of intra-abdominal fat content.[63-65]

Conversely, others have tried to find explanations for the occurrence of the obesity paradox, which was first recognized in chronic disease populations. Moreover, the obesity paradox has also been described in the general population.[19,60] Studies of BMI and cause-specific mortality in the

general population, excluding persons with prior cardiovascular disease, cancer and chronic obstructive pulmonary disease (COPD), revealed that overweight was not associated with an increased risk of cancer or cardiovascular disease, and appeared to be relatively protective for survival.[66] However, excess mortality in the obese population was mainly attributable to cardiovascular disease and obesity-related cancers, including colon cancer, breast cancer, esophageal cancer, pancreatic cancer, uterine cancer, ovarian cancer and kidney cancer.[66,67] In contrast, upper aerodigestive cancers, COPD and other respiratory diseases could explain excess mortality in the underweight population.[66,67] Chronic diseases, including cardiovascular disease, cancer and COPD, are characterized by wasting and increased inflammatory responses, thereby offering possible explanations for the obesity paradox, which causation is probably multi-factorial.

The benefits of obesity

Adipose tissue is a potential endocrine organ capable of secreting a variety of cytokines with opposing actions.[4] Tumor necrosis factor-α (TNF-α) is a pro-inflammatory and atherogenic macrophage-derived cytokine, and is known to promote cardiac and endothelial injury through its apoptotic and

negative inotropic effects.[68] Adipocytes release soluble TNF-α receptors, which can neutralize TNF-α in various inflammatory wasting states.[69] Moreover, adipocytes secrete adipokines, of which adiponectin plays a key role in regulating inflammation and endovascular homeostasis and increasing insulin sensitivity in peripheral tissues.[70] Particularly visceral (abdominal) adiposity is associated with chronic inflammation, insulin resistance and enhanced progression of atherosclerosis.[4] On the other hand, peripheral (lower-body) fat has a protective effect.[71] These differences between visceral and peripheral adiposity are irrespective of gender.[71] However, since BMI cannot distinguish between visceral and peripheral adiposity, this might offer an explanation for the observed survival benefit in the obese population.

Inflammatory responses in obesity can also be reduced by the toxin-scavenging ability of adiposity. Lipopolysaccharides (LPS) are potent endotoxins that induce the release of pro-inflammatory cytokines.[72] Plasma concentrations of LPS are higher in chronic debilitating disorders.[73-75] In overweight and obesity the negative effects of lipopolysaccharides are neutralized by the toxin-scavenging effect of adiposity, in which lipophilic end products of increased catabolism are sequestrated.[57] Furthermore, increased levels of lipoproteins, which are often observed in overweight and obesity, may offer a survival advantage in chronic diseases, because lipoproteins can actively bind to and neutralize circulating endotoxins, the so-called endotoxin-lipoprotein hypothesis.[76]

In addition, the prevalence of cardiovascular risk factors among the overweight and obese has declined in the past decades.[77] Although cardiovascular disease remains the leading cause of death among the obese, this decline in cardiovascular risk factors might have led to a decrease in cardiovascular related mortality, and therefore to a decrease in total mortality.[19] These findings are consistent with declining mortality rates from ischemic heart disease.[78,79] However, it may take several years to decades for obesity and its related cardiovascular disease to have its full impact on mortality.[80] Consequently, in studies without long-term (e.g. more than 15 years) follow-up, the effects of obesity on mortality might have been underestimated, suggesting survival benefit for the obese.

Finally, genetics might offer a different explanation for the survival advantage of the overweight and obese. The thrifty genotype theory is an old theory explaining obesity. This genotype emerged as an adaptive and selective gene-environment interaction in times of famine, and led to obesity when famines no longer occurred in the modern era.[81] This theory would explain the survival advantage of the overweight and obese, however, it is not supported by any substantial scientific evidence.[82] On the other hand, genetic polymorphism in systems related to food intake, energy expenditure and BMI definition can result in variable effects on body composition, which might lead to differential effects on survival among the obese population.[83-85] Figure 2 gives an overview of the multi-factorial causation of the obesity

paradox. In addition to the various aforementioned explanations, there might be currently unknown factors that also contribute to its' causation, as presented in the figure.

The hazards of underweight

The association of increased mortality in the underweight population might, at least in part, be attributable to *reverse causation*, which means that lower weight is not a cause but a result of chronic diseases that are related to poor outcome.[86] Chronic diseases that cause weight loss may remain unnoticed for months or even years, for example, in the case of cancer, chronic respiratory or cardiac diseases. Smoking is another potential confounding factor, because it is associated with both a decreased weight and an increased mortality risk.[86] In order to minimize the effects of reverse causation and smoking on mortality rates, deaths occurring in the initial follow-up period should be disregarded, and analyses should be restricted to patients without preexisting disease and to persons who had never smoked. However, studies that addressed these potential confounders still show increased mortality rates in the underweight population.[18,19,67]

COPD and other respiratory diseases are responsible for the vast majority of mortality in the underweight population.[66,67] This may be due to

weight loss associated with COPD (reverse causation). However, low BMI in COPD has also been shown to be a risk factor for mortality, irrespective of disease severity.[87] In addition, skeletal muscle dysfunction is a common feature in COPD, and can be caused by muscle loss due to wasting and by intrinsic muscular alterations, in which the proportions of skeletal muscle fiber types change.[88] Skeletal muscle dysfunction is recognized to be an independent predictor of mortality in patients with COPD.[89] In underweight patients with COPD the intrinsic muscular alterations are aggravated,[90] and this could also explain the increased mortality risk in this group.

Wasting and inflammation could offer additional explanations for the mortality hazard of the underweight population. Improper nutrition and wasting in chronic illness can result in catabolic changes in skeletal muscle in lean subjects having minimal stores of fat, leading to cachexia.[91] Oxidative stress may be an important underlying cause for both wasting and inflammation.[92] Accumulation of oxidants results from a reduction in anti-oxidant capacity in the face of elevated metabolic requirements. These oxidants have pro-inflammatory effects, which eventually will lead to fatal complications. This cascade is called the "*malnutrition-inflammatory-cachexia complex*".[93] The deleterious effects of the malnutrition-inflammatory-cachexia complex occur rapidly, and the short-term risks of underweight outweigh the long-term (cardiovascular) risks associated with obesity.[93] The malnutrition-inflammatory-cachexia complex clearly explains

the increased mortality risk in the underweight population.

Implications for the surgical population

As previously described, the obesity paradox has also been shown in the surgical population. The mechanisms explaining the survival benefit of the obese in the general population might also be applicable to the obese surgical patient. Moreover, it is speculated that overweight and mild obese patients have a more appropriate inflammatory and immune response to the stress of surgery than their leaner and morbid obese counterparts.[26,27] There is a close relationship between the immune and metabolic response systems, and proper function of each is dependent on the other.[94] Compared to normal weight patients, overweight and obese patients have a more sufficient nutritional reserve and might be functioning in a more efficient metabolic state, and as a result, the inflammatory and immune response to surgery might be more adequate. In contrast, both underweight and morbid obese patients are inefficient in energy expenditure, due to underlying malnutrition and metabolic excess. The inflammatory response to the stress of surgery is aggravated, which leads to further metabolic dysfunction and immunosuppression. Consequently, these patients suffer from adverse outcomes following surgery.[26,27]

In addition, recent weight loss of more than 10% of body weight and lower mean albumin levels, due to protein-energy malnutrition, are common in underweight patients and are indicators of malnourishment. Both conditions are well-known risk factors for adverse outcomes following surgery.[95-98] Several nutrition-screening tools can adequately assess malnourishment, and are able to identify patients who should benefit from nutritional support.[99] Peri- and postoperative nutritional support in malnourished underweight patients can improve outcomes following major surgery.[100-103] On the other hand, preoperative nutritional support in obese patients is not recommended,[101,102] although in obese patients nutritional deficiencies like iron deficiency, resulting in a higher prevalence of anaemia, are common.[21] Weight loss in obese patients prior to surgery is not recommended as well, because studies that evaluated this strategy showed conflicting evidence regarding postoperative outcomes.[21] In obese patients undergoing surgery, the highest priority should be on the recognition and adequate treatment of underlying cardiopulmonary comorbidities that negatively influence postoperative outcomes, including obstructive sleep apnea syndrome, in order to reduce postoperative complications.[21]

Conclusion

Despite the feeling that obese patients requiring surgery are at increased risk for adverse postoperative outcomes, surgery can be relatively safely performed in the higher BMI categories. However, patients at the extremes of BMI, both the underweight and the obese class III, seem to have the highest postoperative morbidity and mortality hazard, which even persists at long-term. The inverse relationship between BMI and mortality is referred to as the obesity paradox, and has been observed both in the general population as well as in several disease specific populations. Cancer and respiratory diseases, including COPD, are responsible for excess mortality in the underweight population, exerting its effects at relatively 'short' long-term, i.e. within years. On the other hand, cardiovascular disease accounts for the majority of deaths among the obese, particularly at longer follow-up. Cancer, COPD and cardiovascular disease are characterized by wasting and inflammation, thereby offering possible explanations for the obesity paradox. Moreover, it is important to consider that BMI is not a measure of body fat distribution. Likely, the cause of the obesity paradox is multi-factorial. It is suggested that future research should be directed at more accurate indices of body fat, such as waist circumference or computed tomographic measurement of intra-abdominal fat content and its' relation with inflammation, in order to examine the association with survival and to

evaluate whether the obesity paradox remains valid, not only in the general population, but also in disease specific populations. This provides more insight into the hazards of both underweight and (morbid) obesity and might lead to a more tailored approach, including dietary and drug strategies, in order to improve outcomes for patients at the extremes of BMI.

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Conflicts of interest

The authors declare no conflicts of interest for the current manuscript.

References

1. Hawn MT, Bian J, Leeth RR, et al. Impact of obesity on resource utilization for general surgical procedures. *Ann Surg* 2005;241(5):821-6.

2. Ward SA, Parikh S, Workman B. Health perspectives: international epidemiology of ageing. *Best Pract Res Clin Anaesthesiol* 2011;25(3):305-17.

3. Liu JH, Etzioni DA, O'Connell JB, Maggard MA, Ko CY. The increasing workload of general surgery. *Arch Surg* 2004;139(4):423-8.

4. Haslam DW, James WP. Obesity. *Lancet* 2005;366(9492):1197-209.

5. Stefan M, Iglesia Lino L, Fernandez G. Medical consultation and best practices for preoperative evaluation of elderly patients. *Hosp Pract (Minneap)* 2011;39(1):41-51.

6. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;854:1-452.

7. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i-xii, 1-253.

8. Lucreziotti S, Foroni C, Fiorentini C. Perioperative myocardial infarction in noncardiac surgery: the diagnostic and prognostic role of cardiac troponins. *J Intern Med* 2002;252(1):11-20.

9. Dunkelgrun M, Schreiner F, Schockman DB, et al. Usefulness of preoperative oral glucose tolerance testing for perioperative risk stratification in patients scheduled for elective vascular surgery. *Am J Cardiol* 2008;101(4):526-9.

10. Ryding AD, Kumar S, Worthington AM, Burgess D. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology* 2009;111(2):311-9.

11. Wu WC, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA* 2007;297(22):2481-8.

12. Poldermans D, Bax JJ, Boersma E, et al. European Society of Cardiology Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J* 2009;30(22):2769-812.

13. Kehlet H, Mythen M. Why is the surgical high-risk patient still at risk? *Br J Anaesth* 2011;106(3):289-91.

14. Barnett S, Moonesinghe SR. Clinical risk scores to guide perioperative management. *Postgrad Med J* 2011;87(1030):535-41.

15. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart

Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;113(6):898-918.

16. Bogers RP, Bemelmans WJ, Hoogenveen RT, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med* 2007;167(16):1720-8.

17. Pascual M, Pascual DA, Soria F, et al. Effects of isolated obesity on systolic and diastolic left ventricular function. *Heart* 2003;89(10):1152-6.

18. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363(23):2211-9.

19. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005;293(15):1861-7.

20. Flum DR, Belle SH, King WC, et al. Longitudinal Assessment of Bariatric Surgery Consortium. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009;361(5):445-54.

21. De Hert S, Imberger G, Carlisle J, et al. Preoperative evaluation of the adult patient undergoing non-cardiac surgery: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2011;28(10):684-722.

22. Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. *Lancet* 2003;361(9374):2032-5.

23. Giles KA, Hamdan AD, Pomposelli FB, et al. Body mass index: surgical site infections and mortality after lower extremity bypass from the National Surgical Quality Improvement Program 2005-2007. *Ann Vasc Surg* 2010;24(1):48-56.

24. Giles KA, Wyers MC, Pomposelli FB, et al. The impact of body mass index on perioperative outcomes of open and endovascular abdominal aortic aneurysm repair from the National Surgical Quality Improvement Program, 2005-2007. *J Vasc Surg* 2010;52(6):1471-7.

25. Morgan MA, Lewis WG, Hopper AN, et al. Prognostic significance of body mass indices for patients undergoing esophagectomy for cancer. *Dis Esophagus* 2007;20(1):29-35.

26. Mullen JT, Davenport DL, Hutter MM, et al. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. *Ann Surg Oncol* 2008;15(8):2164-72.

27. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg* 2009;250(1):166-72.

28. Kulig J, Sierzega M, Kolodziejczyk P, et al. Implications of overweight in gastric cancer: A multicenter study in a Western patient population. *Eur J Surg Oncol* 2010;36(10):969-76.

29. Tokunaga M, Hiki N, Fukunaga T, et al. Better 5-year survival rate following curative gastrectomy in overweight patients. *Ann Surg Oncol* 2009;16(12):3245-51.

30. Tsai S, Choti MA, Assumpcao L, et al. Impact of obesity on perioperative outcomes and survival following pancreaticoduodenectomy for pancreatic cancer: a large single-institution study. *J Gastrointest Surg* 2010;14(7):1143-50.

31. Reeves BC, Ascione R, Chamberlain MH, Angelini GD. Effect of body mass index on early outcomes in patients undergoing coronary artery bypass surgery. *J Am Coll Cardiol* 2003;42(4):668-76.

32. Shirzad M, Karimi A, Armadi SH, et al. Effects of body mass index on early outcome of coronary artery bypass surgery. *Minerva Chir* 2009;64(1):17-23.

33. Habib RH, Zacharias A, Schwann TA, et al. Effects of obesity and small body size on operative and long-term outcomes of coronary artery bypass surgery: a propensity-matched analysis. *Ann Thorac Surg* 2005;79(6):1976-86.

34. Prabhakar G, Haan CK, Peterson ED, et al. The risks of moderate and extreme obesity for coronary artery bypass grafting outcomes: a study from the Society of Thoracic Surgeons' database. *Ann Thorac Surg* 2002;74(4):1125-30; discussion 30-1.

35. Birkmeyer NJ, Charlesworth DC, Hernandez F, et al. Obesity and risk of adverse outcomes associated with coronary artery bypass surgery. Northern New England Cardiovascular Disease Study Group. *Circulation* 1998;97(17):1689-94.

36. Engel AM, McDonough S, Smith JM. Does an obese body mass index affect hospital outcomes after coronary artery bypass graft surgery? *Ann Thorac Surg* 2009;88(6):1793-800.

37. Oreopoulos A, Padwal R, Norris CM, et al. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring)* 2008;16(2):442-50.

38. Potapov EV, Loebe M, Anker S, et al. Impact of body mass index on outcome in patients after coronary artery bypass grafting with and without valve surgery. *Eur Heart J* 2003;24(21):1933-41.

39. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349(9064):1498-504.

40. Menotti A, Blackburn H, Kromhout D, et al. Cardiovascular risk factors as determinants of 25-year all-cause mortality in the seven countries study. *Eur J Epidemiol* 2001;17(4):337-46.

41. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003;63(3):793-808.

42. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004;43(8):1439-44.

43. Kovesdy CP, Anderson JE. Reverse epidemiology in patients with chronic kidney disease who are not yet on dialysis. *Semin Dial* 2007;20(6):566-9.

44. Horwich TB, Fonarow GC. Reverse epidemiology beyond dialysis patients: chronic heart failure, geriatrics, rheumatoid arthritis, COPD, and AIDS. *Semin Dial* 2007;20(6):549-53.

45. Galal W, van Gestel YR, Hoeks SE, et al. The obesity paradox in patients with peripheral arterial disease. *Chest* 2008;134(5):925-30.

46. Butler J, Howser R, Portner PM, Pierson RN, 3rd. Body mass index and outcomes after left ventricular assist device placement. *Ann Thorac Surg* 2005;79(1):66-73.

47. Del Prete JC, Bakaeen FG, Dao TK, et al. The impact of obesity on long-term survival after coronary artery bypass grafting. *J Surg Res* 2010;163(1):7-11.

48. Rahmanian PB, Adams DH, Castillo JG, et al. Impact of body mass index on early outcome and late survival in patients undergoing coronary artery bypass grafting or valve surgery or both. *Am J Cardiol* 2007;100(11):1702-8.

49. Badheka AO, Rathod A, Kizilbash MA, et al. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *Am J Med* 2010;123(7):646-51.

50. Buettner HJ, Mueller C, Gick M, et al. The impact of obesity on mortality in UA/non-ST-segment elevation myocardial infarction. *Eur Heart J* 2007;28(14):1694-701.

51. Diercks DB, Roe MT, Mulgund J, et al. The obesity paradox in non-ST-segment elevation acute coronary syndromes: results from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines Quality Improvement Initiative. *Am Heart J* 2006;152(1):140-8.

52. Guenette JA, Jensen D, O'Donnell DE. Respiratory function and the obesity paradox. *Curr Opin Clin Nutr Metab Care* 2010;13(6):618-24.

53. Landi F, Onder G, Gambassi G, et al. Body mass index and mortality among hospitalized patients. *Arch Intern Med* 2000;160(17):2641-4.

54. Oreopoulos A, Padwal R, Kalantar-Zadeh K, et al. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008;156(1):13-22.

55. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368(9536):666-78.

56. Tremblay A, Bandi V. Impact of body mass index on outcomes following critical care. *Chest* 2003;123(4):1202-7.

57. Kalantar-Zadeh K, Kopple JD. Obesity paradox in patients on maintenance dialysis. *Contrib Nephrol* 2006;151:57-69.

58. Singh JA, Sperling JW, Cofield RH. Ninety day mortality and its predictors after primary shoulder arthroplasty: an analysis of 4,019 patients from 1976-2008. *BMC Musculoskelet Disord* 2011;12:231.

59. Zheng W, McLerran DF, Rolland B, et al. Association between body-mass index and risk of death in more than 1 million Asians. *N Engl J Med* 2011;364(8):719-29.

60. Orpana HM, Berthelot JM, Kaplan MS, et al. BMI and mortality: results from a national longitudinal study of Canadian adults. *Obesity (Silver Spring)* 2010;18(1):214-8.

61. Gallagher D, Visser M, Sepulveda D, et al. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996;143(3):228-39.

62. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)* 2008;32(6):959-66.

63. Schneider HJ, Friedrich N, Klotsche J, et al. The predictive value of different measures of obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab* 2010;95(4):1777-85.

64. Jacobs EJ, Newton CC, Wang Y, et al. Waist circumference and all-cause mortality in a large US cohort. *Arch Intern Med* 2010;170(15):1293-301.

65. Welborn TA, Dhaliwal SS. Preferred clinical measures of central obesity for predicting mortality. *Eur J Clin Nutr* 2007;61(12):1373-9.

66. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007;298(17):2028-37.

67. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373(9669):1083-96.

68. Ferrari R. The role of TNF in cardiovascular disease. *Pharmacol Res* 1999;40(2):97-105.

69. Mohamed-Ali V, Goodrick S, Bulmer K, et al. Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. *Am J Physiol* 1999;277(6 Pt 1):E971-5.

70. Hopkins TA, Ouchi N, Shibata R, Walsh K. Adiponectin actions in the cardiovascular system. *Cardiovasc Res* 2007;74(1):11-8.

71. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes (Lond)* 2010;34(6):949-59.

72. Raetz CR, Whitfield C. Lipopolysaccharide endotoxins. *Annu Rev Biochem* 2002;71:635-700.

73. Lassenius MI, Pietilainen KH, Kaartinen K, et al. Bacterial endotoxin activity in human serum is associated with dyslipidemia, insulin resistance, obesity, and chronic inflammation. *Diabetes Care* 2011;34(8):1809-15.

74. Szeto CC, Kwan BC, Chow KM, et al. Endotoxemia is related to systemic inflammation and atherosclerosis in peritoneal dialysis patients. *Clin J Am Soc Nephrol* 2008;3(2):431-6.

75. Niebauer J, Volk HD, Kemp M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet* 1999;353(9167):1838-42.

76. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet* 2000;356(9233):930-3.

77. Gregg EW, Cheng YJ, Cadwell BL, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA* 2005;293(15):1868-74.

78. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ* 2012;344:d8059.

79. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999;353(9164):1547-57.

80. Dyer AR, Stamler J, Garside DB, Greenland P. Long-term consequences of body mass index for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. *Ann Epidemiol* 2004;14(2):101-8.

81. Prentice AM. Early influences on human energy regulation: thrifty genotypes and thrifty phenotypes. *Physiol Behav* 2005;86(5):640-5.

82. Paradies YC, Montoya MJ, Fullerton SM. Racialized genetics and the study of complex diseases: the thrifty genotype revisited. *Perspect Biol Med* 2007;50(2):203-27.

83. Farooqi IS, Keogh JM, Yeo GS, et al. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med* 2003;348(12):1085-95.

84. Loktionov A. Common gene polymorphisms and nutrition: emerging links with pathogenesis of multifactorial chronic diseases (review). *J Nutr Biochem* 2003;14(8):426-51.

85. Farooqi S, O'Rahilly S. Genetics of obesity in humans. *Endocr Rev* 2006;27(7):710-18.

86. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med* 1999;341(6):427-34.

87. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350(10):1005-12.

88. Gosker HR, Zeegers MP, Wouters EF, Schols AM. Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax* 2007;62(11):944-9.

89. Swallow EB, Reyes D, Hopkinson NS, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 2007;62(2):115-20.

90. Gosker HR, van Mameren H, van Dijk PJ, et al. Skeletal muscle fibre-type shifting and metabolic profile in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002;19(4):617-25.

91. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr* 2006;83(4):735-43.

92. Himmelfarb J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. *Semin Dial* 2009;22(6):636-43.

93. Kalantar-Zadeh K. Recent advances in understanding the malnutrition-inflammation-cachexia syndrome in chronic kidney disease patients: What is next? *Semin Dial* 2005;18(5):365-9.

94. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444(7121):860-7.

95. Windsor JA, Hill GL. Weight loss with physiologic impairment. A basic indicator of surgical risk. *Ann Surg* 1988;207(3):290-6.

96. Palma S, Cosano A, Mariscal M, et al. Cholesterol and serum albumin as risk factors for death in patients undergoing general surgery. *Br J Surg* 2007;94(3):369-75.

97. Gibbs J, Cull W, Henderson W, et al. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg* 1999;134(1):36-42.

98. Hennessey DB, Burke JP, Ni-Dhonochu T, et al. Preoperative hypoalbuminemia is an independent risk factor for the development of surgical site infection following gastrointestinal surgery: a multi-institutional study. *Ann Surg* 2010;252(2):325-9.

99. Anthony PS. Nutrition screening tools for hospitalized patients. *Nutr Clin Pract* 2008;23(4):373-82.

100. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg* 2002;137(2):174-80.

101. Klek S, Sierzega M, Szybinski P, et al. Perioperative nutrition in malnourished surgical cancer patients - a prospective, randomized, controlled clinical trial. *Clin Nutr* 2011;30(6):708-13.

102. Braga M, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Parenteral Nutrition: surgery. *Clin Nutr* 2009;28(4):378-86.

103. Weimann A, Braga M, Harsanyi L, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. *Clin Nutr* 2006;25(2):224-44.

Table 1 BMI classification according to the WHO[6]

	BMI (kg/m^2)
Underweight	< 18.5
Normal	18.5 – 24.9
Overweight (pre-obese)	25.0 – 29.9
Obese	≥ 30.0
Obese class I (mild obese)	30.0 – 34.9
Obese class II (moderate obese)	35.0 – 39.9
Obese class III (morbid obese)	≥ 40.0

BMI Body Mass Index; WHO World Health Organization

Table 2 Populations showing the obesity paradox

Non-surgical Populations	Surgical Populations
Cardiac Disease	**Vascular surgery**
Acute coronary syndromes[50,51]	Peripheral arterial disease[23,45]
Percutaneous coronary interventions (PCI)[37]	Abdominal aortic aneurysm[24]
Coronary artery disease[55]	
Chronic atrial fibrillation[49]	**Cancer surgery**
Chronic heart failure[44,54]	Pancreaticoduodenectomy[30]
	Gastrectomy[29]
Chronic obstructive pulmonary disease[44,52]	
	Orthopedic surgery
Renal disease	Arthroplasty[58]
Chronic kidney disease[43]	
Maintenance dialysis[57]	**Cardiac surgery**
	Coronary artery bypass grafting[31,32,34,36-38]
Rheumatoid arthritis[44]	Left-ventricular assist device placement[46]
Acquired immunodeficiency[44]	
Intensive care unit patients[56]	
Hospitalized patients[53]	
Advanced age[44]	

Legends to Figures

Figure 1. Odds ratios (adjusted) for 30-day mortality after (non-bariatric) general surgery displayed by obesity class, with normal BMI class used as reference. (Adapted with permission from Mullen et al, Ann Surg 2009 [22]).

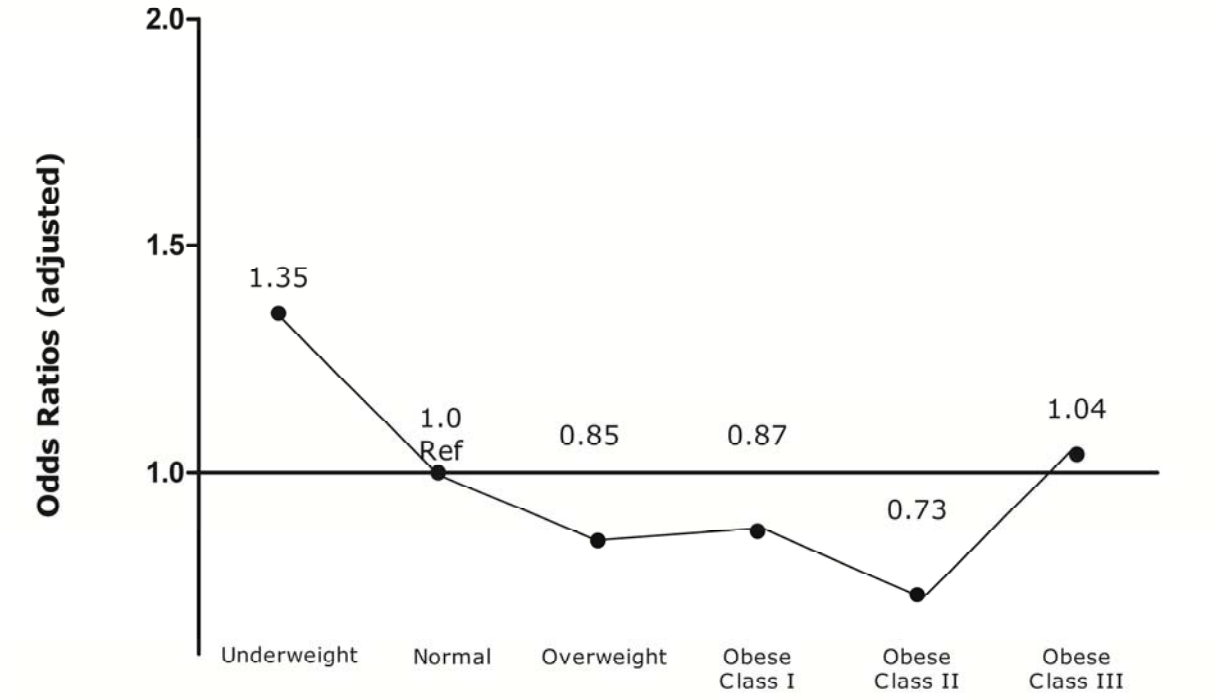
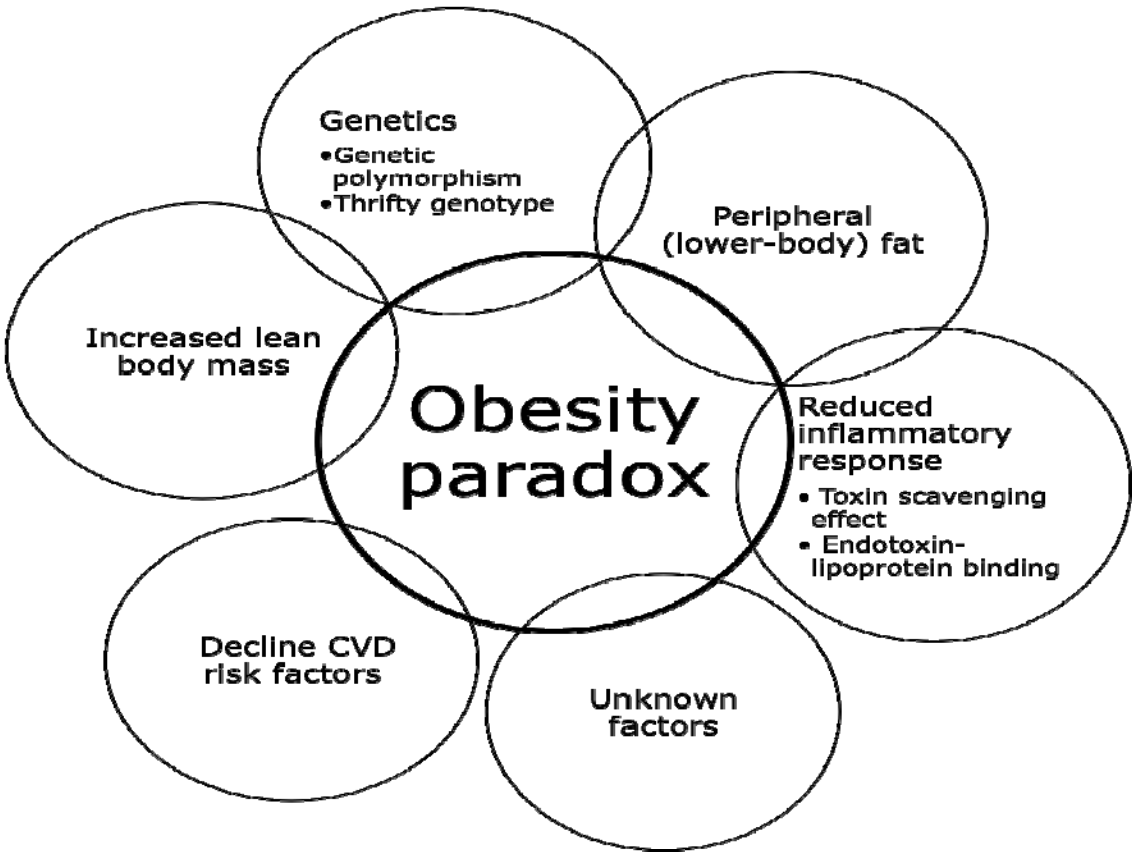
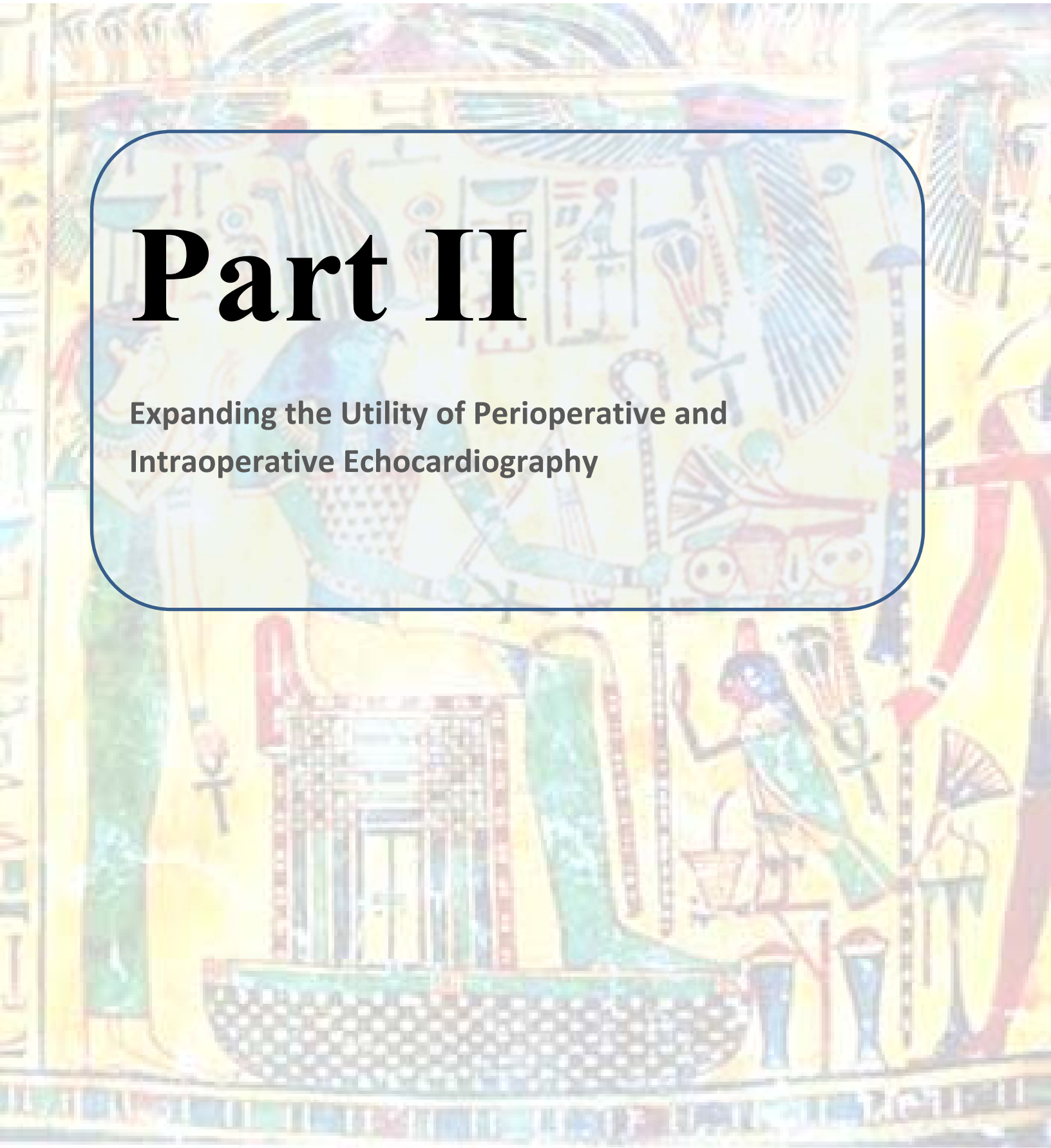


Figure 2. Schematic representation of possible causes of the obesity paradox, showing its' multi-factorial origin with several (overlapping) hypotheses.

CVD = cardiovascular disease.





Part II

Expanding the Utility of Perioperative and Intraoperative Echocardiography

CHAPTER 6

Relation between Preoperative and Intraoperative New Wall Motion Abnormalities in Vascular Surgery Patients: A Transesophageal Echocardiographic Study

Anesthesiology 2010; 112(3): 557-66

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Prevalence and Pharmacological Treatment of Left-ventricular Dysfunction in Patients undergoing Vascular Surgery

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ABSTRACT

Aims. This study evaluated the prevalence of left-ventricular (LV) dysfunction in vascular surgery patients and pharmacological treatment, according ESC guidelines.

Methods. Echocardiography was performed preoperatively in 1,005 consecutive patients. Left-ventricular ejection fraction (LVEF) ≤50% defined systolic LV dysfunction. Diastolic LV dysfunction was diagnosed based on E/A-ratio, pulmonary vein flow, and deceleration time. Optimal pharmacological treatment to improve LV function was considered as: (i) angiotensin-blocking agent (ACE-I/ABR) in patients with LVEF ≤40%; (ii) ACE-I/ABR and β-blocker in patients with LVEF ≤40% + heart failure symptoms or previous myocardial infarction; and (iii) a diuretic in patients with symptomatic heart failure, regardless of LVEF.

Results. Left-ventricular dysfunction was present in 506 patients (50%), of whom 209 (41%) had asymptomatic diastolic LV dysfunction, 194 (39%) had asymptomatic systolic LV dysfunction, and 103 (20%) had symptomatic heart failure. Treatment with ACE-I/ABR and/or β-blocker could be initiated/improved in 67 (34%) of the 199 patients with asymptomatic LVEF ≤40%. A diuretic could be initiated in 32 patients (31%) with symptomatic heart failure (regardless of LVEF).

Conclusion. This study demonstrated a high prevalence of LV dysfunction in vascular surgery patients and under-utilization of ESC recommended pharmacological treatment. Standard preoperative evaluation of LV function could be argued based on our results to reduce this observed care gap.

INTRODUCTION

Patients undergoing vascular surgery are known to be at increased risk of perioperative complications due to frequently underlying (a)symptomatic coronary artery disease. Coronary artery disease is the aetiology of heart failure in 60–70% of patients, predominantly in the elderly population.[1, 2]. Coupled to the growing prevalence of heart failure and the elderly population, is the increase in surgical procedures. In addition, many invasive surgical interventions (such as major vascular surgery) are increasingly performed in elderly patients. Worldwide, about 100 million adults undergo noncardiac surgery every year and by the year 2020 the number of patients eligible for surgery will increase by 25%, with the largest group of patients aged >65 years.[3]

Considerable improvements have been made in the treatment of heart failure. Guidelines of the European Society of Cardiology (ESC) recommend treatment with angiotensin-converting enzyme inhibitors (ACE-I) in patients with systolic left-ventricular (LV) dysfunction, defined as LV ejection fraction (LVEF) ≤40%, irrespective of the presence of heart failure symptoms to improve ventricular function.[4] An angiotensin-receptor blocker (ARB) is recommended in case of ACE-I intolerance.[4] Patients with asymptomatic systolic LV dysfunction and a myocardial infarction (MI) in past history are recommended to receive a β-blocker as well. A diuretic is recommended next to these agents in patients with symptomatic heart failure.[4]

The aim of the current study was to evaluate the prevalence and pharmacological treatment for asymptomatic systolic LV dysfunction or

symptomatic heart failure, according to the ESC guidelines, in the vascular surgery population and the impact of treatment on late outcome.

METHODS

Study population and baseline characteristics

The patient population consisted of 1,005 consecutive vascular surgery patients at the Erasmus Medical Center (Rotterdam, the Netherlands) during 2002-2008. The study was approved by the hospital's ethics committee and performed with the informed consent of all patients. A detailed history was obtained from every patient and clinical data included age, gender, ischemic heart disease (history of angina pectoris, coronary revascularization, or myocardial infarction), cerebrovascular disease (history of ischemic or hemorrhagic stroke), renal dysfunction (serum creatinine >2 mg/dL), diabetes mellitus (fasting blood glucose ≥7.0 mmol/L or requirement for anti-diabetic medication), hypertension (blood pressure ≥140/90 mmHg in non-diabetics and ≥130/80 mmHg in diabetics or requirement for antihypertensive medication), dyslipoproteinemia (low-density lipoprotein cholesterol >3,50 mmol/L or requirement of lipid-lowering medication) and chronic obstructive pulmonary disease.

Left-ventricular dysfunction

Preoperatively, transthoracic echocardiography was performed in all patients using a handheld Acuson Cypress Ultrasound System (7V3c transducer). Standard images were obtained at rest with the patient in the left lateral decubitus position as recommended.[5] Left-ventricular end-systolic and end-

diastolic volumes were determined and LVEF was calculated using the biplane Simpson's technique.[6] Systolic (S) and diastolic (D) pulmonary vein flow, deceleration time, and mitral inflow E/A ratios of peak velocities (at early rapid filling E and late filling due to atrial contraction A) were determined in apical 4-chamber view as recommended [7]. An LVEF ≤50% was defined as reduced and an LVEF ≤40% was eligible for pharmacological treatment.[4] Diastolic LV dysfunction was confirmed in patients with E/A-ratio <0.8 or >2.[8] Abnormal pulmonary vein flow (S/D <1) was used to distinguish normal and pseudo-normal diastolic LV function in patients with E/A-ratio between 0.8 and 2.[9] Deceleration time >220 or <140 ms defined diastolic LV dysfunction in patients with atrial fibrillation.[9] Patients with both systolic and diastolic LV dysfunction were classified as systolic LV dysfunction. The presence of LV dysfunction in combination with heart failure symptoms (shortness of breath, fatigue, exercise intolerance, signs of fluid retention)[4] defined symptomatic heart failure. Two experienced investigators performed off-line assessments of the obtained ultrasound images. When there was disagreement between the two assessors, a third investigator viewed the images without knowledge of the previous assessment and a majority decision was reached.

European Society of Cardiology treatment recommendations

During the first preoperative visit to the outpatient clinic, the use of the prescription medications was recorded and included ACE-Is, ARBs, β-blockers, diuretics, statins, aspirin, oral anticoagulants, and nitrates. In the current study the following ESC treatment recommendations were used: (i) treatment of all patients with an LVEF ≤40% with at least ACE-I/ARB, (ii) treatment of patients with an LVEF ≤40% and a history of myocardial infarction with ACE-I/ARB and a β-blocker, (iii) treatment of heart failure

symptoms with a diuretic, regardless of LVEF, and (iv) treatment of LVEF ≤40% in combination with heart failure symptoms with ACE-I/ARB in combination with a β-blocker and diuretic.

Contraindications for ACE-I/ARB were confirmed in patients with known ACE-I/ARB intolerance, history of angio-oedema, bilateral renal artery stenosis, serum potassium concentration >5.0 mmol/L, serum creatinine >2.5 mg/dL, and severe aortic stenosis.[4] Contraindications for β-blocker treatment were confirmed in patients with known β-blocker intolerance, sinus bradycardia <50 beats per minute, second- or third degree heart block, sick sinus syndrome, or asthma.[4] In addition, contraindication for diuretic treatment was confirmed in patients with known diuretic intolerance, renal failure, clinical signs of hypovolemia or dehydration, serum potassium concentration <3.5 mmol/L, serum magnesium concentration <1.2 mmol/L, or serum sodium concentration <135 mmol/L.[4]

Follow-up

Long-term mortality was assessed by approaching the municipal civil registries. Survival status and medication use was completed by approaching the referring physician. All surviving patients received a mailed questionnaire (80% response rate) addressing medication use. Medication use in patients who died or patients who did not respond the questionnaire, was completed by approaching the referring physician. Mean follow-up was 2.2 ± 1.8 years.

Statistical analysis

Dichotomous data are presented as numbers and percentages and categorical data are compared using the χ^2 test. The continuous variables age, blood

pressure, and heart rate are described as means ± standard deviation (SD) and compared using ANOVA. The relation between ACE-I/ARB use in patients with an LVEF ≤40% and long-term mortality was evaluated with Cox regression analyses with propensity score adjustment for treatment with ACE-I/ARB. Multivariate analyses were adjusted for demographics (age and gender), cardiovascular risk factors (ischemic heart disease, cerebrovascular disease, renal dysfunction, diabetes mellitus, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, and smoking status) and medication use (β-blockers, statins, and aspirin). We report (crude and adjusted) hazard ratios with their 95% confidence interval. For all tests, a *p*-value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS version 15.0 statistical software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

The baseline study population consisted of 1,005 vascular surgery patients, of which the majority were males (77%) and the mean age was 67 (SD ± 10) years. Patients with LV dysfunction were older and more often male compared with patients with normal LV function. In addition, LV dysfunction was associated with ischemic heart disease, renal dysfunction, hypertension, and chronic obstructive pulmonary disease (*Table 1*).

Prevalence of left-ventricular dysfunction

Left–ventricular dysfunction was diagnosed in 506 (50%) patients (*Figure 1*), of which 403 (80%) patients had asymptomatic LV dysfunction and 103 (20%)

patients had symptomatic heart failure. Of the patients with asymptomatic LV dysfunction, 209 (52%) had asymptomatic isolated diastolic LV dysfunction and 194 (48%) had asymptomatic systolic LV dysfunction. In total, 130 (67%) patients with asymptomatic systolic LV dysfunction had an LVEF ≤40% (*Figure 2*). In this group, a medical history of myocardial infarction could be appointed as a cause of LV dysfunction in 63 (49%) patients. In addition, valvular stenosis and/or regurgitation could be appointed in 33 (25%) patients as a possible cause of LV dysfunction.

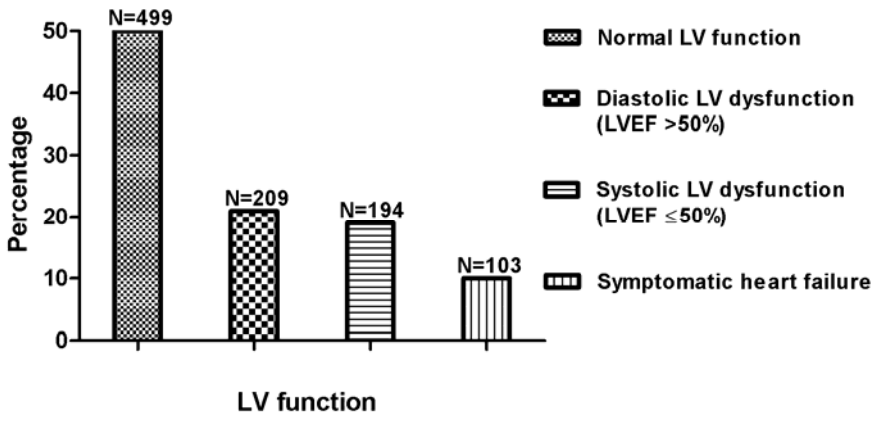
Of the 103 patients with symptomatic heart failure, 72 (70%) patients had NYHA II, 28 (27%) patients had NYHA III, and 3 (3%) patients had NYHA IV. In addition, 69 (67%) patients had an LVEF ≤40%. In this group, a medical history of myocardial infarction could be appointed as a cause of LV dysfunction in 52 (75%) patients. In addition, valvular stenosis and/or regurgitation could be appointed in 10 (15%) patients as a possible cause of LV dysfunction.

Table 1 **Baseline characteristics according left-ventricular function**

	Normal LV function	**LV dysfunction**	***p*-value**
	[N=499]	[N=506]	
Demographics			
Age in years (± SD)	65 (11)	70 (10)	<0.01
Male (%)	363 (73)	406 (80)	0.005
Medical history (%)			
Ischemic heart disease	165 (33)	265 (52)	<0.01
Cerebrovascular disease	169 (34)	184 (36)	0.407
Renal dysfunction	61 (12)	114 (23)	<0.01
Diabetes mellitus	98 (20)	117 (23)	0.178
Hypertension	294 (59)	364 (72)	<0.01
Hypercholesterolemia	233 (47)	249 (49)	0.425
Chronic obstructive pulmonary disease	145 (29)	222 (44)	<0.01

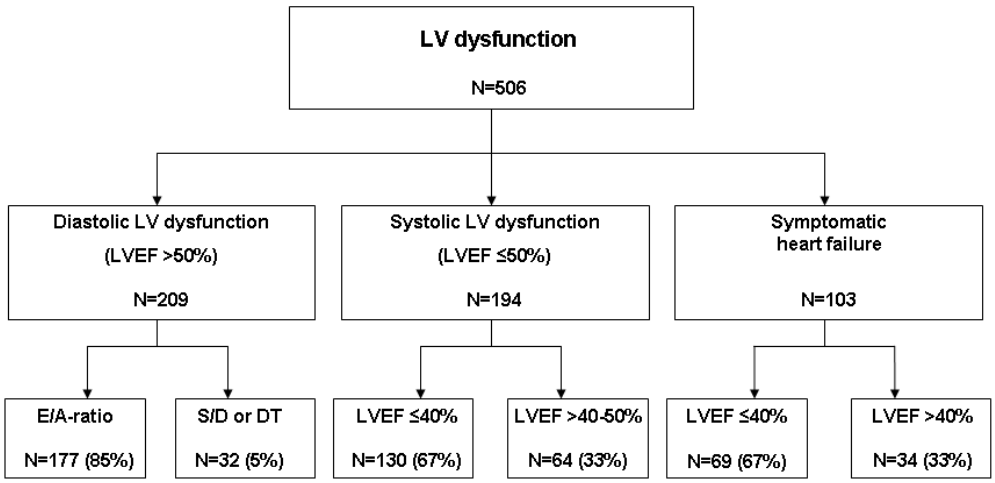
Left-ventriccular (LV), standard deviation (SD).

Figure 1: Prevalence of left-ventricular function in patients undergoing vascular surgery.



Left-ventricular (LV), left-ventricular ejection fraction (LVEF).

Figure 2: Distribution of the different types of left-ventricular dysfunction.



Deceleration time (DT), left-ventricular (LV), left-ventricular ejection fraction (LVEF).

Pharmacological treatment at first presentation

Medication use was recorded during the first presentation at the outpatient clinic. Most frequently, we observed the use of (i) statins (N=527 or 52%), (ii) aspirin (N=430 or 43%) (iii) β-blockers (N=366 or 36%), (iv) ACE-I (N=310 or 31%), (v) diuretics (N=253 or 25%) (vi) oral anticoagulants (N=164 or 16%), (vii) ARB (N=144 or 14%) and (viii) nitrates (N=101 or 10%). Medication use stratified according to LV function is demonstrated in *Table 2*. The use of ACE-I, ARB, β-blockers, diuretics, oral anticoagulants, and nitrates was associated with LV dysfunction.

Table 2 **Medication use stratified according to left-ventricular function at first presentation to the outpatient clinic**

MEDICATION USE (%)	Normal LV function	Diastolic LV dysfunction (LVEF >50%)	Systolic LV dysfunction (LVEF ≥50%)	Symptomatic heart failure	*p* for trend
	[N=499]	[N=209]	[N=194]	[N=103]	
ACE inhibitors	129 (26)	65 (31)	63 (33)	53 (52)	<0.001
Angiotensin-receptor	67 (13)	28 (13)	28 (14)	21 (20)	0.005
β-blockers	138 (28)	80 (38)	81 (42)	67 (65)	<0.001
Diuretics	95 (19)	54 (26)	57 (29)	47 (46)	<0.001
Statins	249 (50)	108 (52)	114 (59)	564 (54)	0.433
Aspirin	165 (33)	83 (40)	102 (53)	80 (78)	<0.001
Oral anticoagulants	61 (12)	35 (17)	41 (21)	27 (26)	<0.001
Nitrates	32 (6)	19 (9)	20 (10)	30 (29)	<0.001

Angiotensin-converting enzyme (ACE), left-ventricular (LV).

Pharmacological treatment to improve left-ventricular function

As demonstrated in *Table 3*, 71 patients with an LVEF ≤40% and NYHA = 1 did not have a myocardial infarction in their past history. Of these patients, 31

(44%) patients received no treatment and 25 (35%) patients received optimal treatment with ACE-I/ARB to improve LV function. In addition, 128 patients with an LVEF ≤40% did have a myocardial infarction and/or had current NYHA ≥2. Of these patients, 31 (24%) patients received no treatment and 52 (41%) patients received optimal treatment with ACE-I/ARB in combination with a β-blocker to improve LV function. Of the patients who received no or suboptimal treatment to improve LV function, 55 (28%) patients had a contraindication to ACE-I/ARB and/or β-blockers. Therefore, pharmacological treatment to improve LV function could be initiated or improved in 67 (34%) of the patients with an LVEF ≤40%.

Table 3	**Patients with left-ventricular ejection fraction ≤40%, treatment with angiotensin blocking agents and β-blockers to improve left-ventricular function**			
LVEF ≤40%			**No previous MI and current NYHA 1** [a]	**Previous MI and/or current NYHA ≥2** [b]
			[N=71]	[N=128]
ABA-	β-blocker -	(%)	31 (44)	31 (24)
ABA+	β-blocker -	(%)	17 (24)	24 (19)
ABA-	β-blocker +	(%)	15 (21)	21 (16)
ABA+	β-blocker +	(%)	8 (11)	52 (41)
Optimal treatment		(%)	25 (35)	52 (41)
Suboptimal treatment	contraindication: no	(%)	9 (13)	24 (19)
	contraindication: yes	(%)	6 (9)	20 (16)
No treatment	contraindication: no	(%)	18 (25)	16 (12)
	contraindication: yes	(%)	13 (18)	15 (12)

[a] *Treatment for LV function should at least contain ABA,* [b] *Treatment for left ventricular function should at least contain an ABA in combination with β-blocker. Angiotensin blocking agent (ABA), left-ventricular ejection fraction (LVEF), myocardial infarction (MI), New York Heart Association (NYHA).*

Pharmacological treatment to reduce heart failure symptoms

In total 103 patients had heart failure symptoms with a severity of NYHA class 2 or more during the first presentation at the outpatient clinic (*Table 4*). Of

these, 47 (46%) patients received a diuretic. After adjustment for contraindications, initiation of diuretic treatment was possible in 32 (31%) of the patients. In addition, of the patients with an LVEF ≤40% and heart failure symptoms NYHA ≥2 (N=65), 19 (29%) patients received optimal treatment with ACE-I/ARB in combination with a β-blocker and a diuretic. Of the patients who received no or suboptimal treatment to reduce heart failure symptoms, 28 (43%) patients had a contraindication to ACE-I/ARB, β-blockers or diuretics. Pharmacological treatment to reduce heart failure symptoms could therefore be initiated or improved in 18 (28%) patients with and an LVEF ≤40% and heart failure symptoms NYHA ≥2.

Table 4 **Patients with symptomatic heart failure, treatment with diuretics for symptom relief**

NYHA ≥2			LVEF ≤40%	LVEF >40%
			[N=68]	[N=35]
Diuretic		(%)	34 (50)	13 (37)
No diuretic	contraindication: no	(%)	18 (26)	14 (40)
	contraindication: yes	(%)	16 (34)	8 (23)

Left-ventricular ejection fraction (LVEF), New York Heart Association (NYHA).

Pharmacological treatment at time of discharge

In total, 199 patients with an LVEF ≤40% were recommended to receive at least ACE-I/ARB treatment to improve their LV function. Of these patients, 139 (70%) patients were treated with an ACE-I/ARB, and 187 (94%) patients with a β-blocker at time of discharge. Multivariate analyses demonstrated that ACE-I/ARB treatment was independently associated with a reduced risk of long-term mortality (HR 0.53, 95%-CI: 0.33 to 0.87).

DISCUSSION

We have found that LV dysfunction was present in around half of the patients undergoing vascular surgery and the majority (80%) of LV dysfunction was asymptomatic. Of the patients with asymptomatic LV dysfunction, around half the patients had asymptomatic systolic LV dysfunction. In addition, we found that in approximately one-third of the patients with LV dysfunction (asymptomatic or symptomatic), pharmacological treatment, as recommended in ESC guidelines, could be initiated or improved.

In countries represented by the ESC, the prevalence of LV dysfunction is suspected to be around 4% in the general population. In septo- and octogenarians, the prevalence is between 10 and 20%.[4] In our sub-population, of patients undergoing vascular surgery (mean age 67 years), we found a prevalence of LV dysfunction of around 50%. With respect to adherence of ESC recommendations, the EuroHeart Failure Survey provided information on the state of implementation of the guidelines.[10] The following prescription rates in patients with LVEF <40% were reported: (i) ACE-I: 80%, (ii) ARB: 6%, (iii) β-blocker: 49% and (iv) diuretics: 88%.[10] Drechsler *et al.* assessed

pharmacological treatment in 747 patients with symptomatic heart failure (LVEF ≤40%) and found that 84% received ACE-I, 72% received ACE-I + β-blocker, and 38% received ACE-I + β-blocker + diuretic.[11]

The above-mentioned studies included patients with symptomatic heart failure and concluded that there is insufficient adherence to the ESC guidelines. All patients included in the present study received routine preoperative echocardiography, which allowed the evaluation of asymptomatic LVEF ≤40% as well. We found that half of the patients with symptomatic LVEF ≤40% and one-third of patients with symptomatic diastolic LV dysfunction received a diuretic. In addition, less than one-third of the patients with symptomatic LVEF ≤40% received an ACE-I/ARB + β-blocker + a diuretic. Therefore, we found that optimal treatment for symptomatic heart failure was lower in our vascular surgery population, compared with the population described by Drechsler *et al.*[11] Understandably, the under-use of ACE-I/ARB and β-blockers was more pronounced in patients with asymptomatic LVEF ≤40%.

Peripheral arterial disease patients have a three to six-fold increased risk for cardiovascular mortality compared with patients without peripheral arterial disease.[12, 13] There is growing awareness of the systemic vascular risk of patients with peripheral arterial disease. However, the Reduction of Atherothrombosis for Continued Health registry demonstrated that peripheral arterial disease patients do not receive adequate risk factor control, compared with individuals with coronary artery or cerebrovascular disease. In addition, it demonstrated that improved risk factors control is associated with a positive impact on 1 year cardiovascular event rates.[14, 15]

In the latest ESC perioperative guidelines, heart failure symptoms are a well-acknowledged risk factor for cardiac events.[16] In addition, preoperative cardiac risk indices identify symptomatic heart failure to be an important risk factor.[17-19] Asymptomatic LV dysfunction is considered a precursor of symptomatic heart failure, which is associated with high mortality.[4] Currently, routine echocardiography is not recommended for preoperative evaluation of LV function. However, echocardiography may be performed in asymptomatic patients undergoing high-risk surgery, such as vascular surgery.[16] We found that one out of four vascular surgery patients were eligible for pharmacological treatment of LV dysfunction,[4] and more than half of these patients appeared to be asymptomatic. With more routine use of preoperative echocardiography in vascular surgery patients, pharmacological treatment of asymptomatic LV dysfunction could be improved.

Based on cost-effectiveness considerations, preoperative echocardiography might not be applicable for all vascular surgery patients. However, these days biochemical markers such as N-terminal pro-B-type natriuretic peptide, are increasingly used to detect or exclude LV dysfunction.[20] Therefore, standard measurements of this biochemical marker may play an important role in detecting asymptomatic LV dysfunction in vascular surgery patients. In patients with increased levels of N-terminal pro-B-type natriuretic peptide, LV dysfunction could be confirmed with echocardiography.

Potential limitations of these data merit consideration. First, although we included 1005 patients, the sample size eligible for ESC recommended treatment was relatively small. Second, although experienced investigators

performed off-line assessments of the ultrasound images, we cannot rule out interobserver variability to have had minor influence on our results. Third, the evaluation of diastolic LV function was limited, not including E/E' ratio, isovolumetric relaxation time, or Tissue Doppler Imaging. Finally, our population consisted of patients referred to a tertiary referral center and may not fully represent the general vascular surgery population.

In conclusion, the current study demonstrates that one-third of vascular surgery patients with LV dysfunction do not receive optimal pharmacological treatment, as recommended in ESC guidelines. More routine use of echocardiography prior to vascular surgery could reduce the observed care gap in vascular surgery patients, with subsequent initiation of ESC recommended pharmacological treatment, and thereby improve late outcome

REFERENCES

1. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J.* 2001;22(3):228-236.

2. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J.* 2003;24(5):442-463.

3. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth.* 2004;18(1):1-6.

4. Dickstein. ESC Guidelines for the diagnosing and treatment of acute and chronic heart failure 2008. *Eur Heart J.* 2008;10:1093.

5. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7(2):79-108.

6. Stamm RB, Carabello BA, Mayers DL, et al. Two-dimensional echocardiographic measurement of Left-ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J.* 1982;104(1):136-144.

7. Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2002;15(2):167-184.

8. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of Left-ventricular diastolic function by echocardiography. *Eur J Echocardiogr.* 2009;10(2):165-193.

9. Persson H, Lonn E, Edner M, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol.* 2007;49(6):687-694.

10. Cleland JG, Swedberg K, Cohen-Solal A, et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. *Eur J Heart Fail.* 2000;2(2):123-132.

11. Drechsler K, Dietz R, Klein H, et al. Euro heart failure survey. Medical treatment not in line with current guidelines. *Z Kardiol.* 2005;94(8):510-515.

12. Hackam DG, Sultan NM, Criqui MH. Vascular protection in peripheral artery disease: systematic review and modelling study. *Heart.* 2009;95(13):1098-1102.

13. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis.* 1991;87(2-3):119-128.

14. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama.* 2006;295(2):180-189.

15. Cacoub PP, Abola MT, Baumgartner I, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis.* 2009;204(2):e86-92.

16. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in noncardiacsurgery: The Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2009.

17. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297(16):845-850.

18. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100(10):1043-1049.

19. Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index. *Am J Med.* 2005;118(10):1134-1141.

20. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. *Cmaj.* 2006;175(6):611-617.

CHAPTER 7

Prevalence and Pharmacological Treatment of Left-Ventricular Dysfunction in Patients Undergoing Vascular Surgery

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The relation between preoperative cardiac stress testing and intraoperative wall motion abnormalities and the impact on postperative outcome: A transesophageal echocardiographic study

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Abstract

Background: Coronary revascularization of suspected culprit coronary lesion assessed by preoperative stress testing is not associated with improved outcome in vascular surgery patients.

Objectives: To study the correlation between the location of the preoperative assessed new wall motion abnormalities (NWMAs) by dobutamine echocardiography (DE) and those assessed by transesophageal echocardiography (TEE) during vascular surgery.

Methods: Fifty-four major vascular surgical patients underwent preoperative DE and intraoperative TEE. The locations of left ventricular (LV) rest wall motion abnormalities and NWMAs were scored using a seven-wall model. During 30-day follow-up, postoperative cardiac troponin release, myocardial infarction and cardiac death were noted.

Results: Rest wall motion abnormalities were noted by DE in 17 patients (31%), and TEE was noted in 16 (30%). NWMAs were induced during DE in 17 patients (31%), whereas NWMAs were observed by TEE in 23 (43%), κ value = 0.65. Although preoperative and intraoperative rest wall motion abnormalities showed an excellent agreement for the location (κ value = 0.92), the agreement for preoperative and intraoperative NWMAs in different locations was poor (κ value = 0.26-0.44). The composite cardiac endpoint occurred in 14 patients (26%).

Conclusions: There was a poor correlation between the locations of preoperatively assessed stress-induced NWMAs by DE and those observed intraoperatively using TEE. However, the composite end-point of outcome was met more frequently in relation with intraoperative NWMAs.

Key words: dobutamine echocardiography, perioperative myocardial ischemia, transesophageal echocardiography, new wall motion abnormalities.

Condensed abstract

The correlation between the locations of preoperative assessed new wall motion abnormalities by dobutamine echocardiography (DE) with intraoperatively assessed new wall motion abnormalities by transesophageal echocardiography (TEE) was studied in patients undergoing major vascular surgery. DE could predict patients who developed postoperative cardiac events. However, poor agreement for the location of ischemia was observed.

Abbreviations

cTnT:	cardiac troponin-T
DE:	dobutamine echocardiography
ECG:	electrocardiography
κ:	kappa estimate (coefficient)
LV:	left ventricular
MAP:	Mean arterial pressure (invasive)
MI:	myocardial infarction
NWMA:	new wall motion abnormality/abnormalities
Rest WMA:	rest wall motion abnormality/abnormalities
TEE:	Transesophageal echocardiography

Introduction:

Vascular surgical patients represent a population at increased risk for developing postoperative (PO) adverse cardiac outcomes. [1, 2] Cardiac stress testing prior to surgery is widely used to identify patients at increased risk of PO cardiac events. Recently, prophylactic coronary revascularization was studied in vascular surgery patients. [3] However, revascularization of the suspected intraoperative culprit coronary lesion, assessed by preoperative testing, was not associated with an improved outcome.

Although, the pathophysiology of perioperative myocardial infarction (MI) is not entirely clear, it is now well accepted that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is an important cause. This is similar to the non-operative setting. The surgical stress response includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability. [4] In patients with significant coronary artery disease (CAD), MI may also be caused by a sustained myocardial supply/demand mismatch due to tachycardia and increased myocardial contractility. The association of PO MI with myocardial ischemia and nontransmural or circumferential subendocardial infarction supports this mechanism. Although, transmural ischemia is considered to be relatively uncommon, half of all fatalities have direct evidence of plaque disruption defined as fissure or rupture of plaque and hemorrhage into the plaque cavity. [5-7]

The use of intraoperative transesophageal echocardiography (TEE) had recognized a high prevalence of transient myocardial ischemic episodes causing regional wall motion abnormalities (WMA) in patients undergoing major non-cardiac surgery and requiring vigilant monitoring for serious cardiac outcomes. [8-10] Those transient events reflect the balancing effects of coronary reserve and myocardial viability versus a multifactorial perioperative ischemic load (burden). Different detection modalities like persantine-thallium scintigraphy and electrocardiography were compared to intraoperative TEE in detecting ischemia with inconclusive results. [11, 12] However, the location of ischemic events has never been a primary goal in all previous investigations.

Our hypothesis is that although dobutamine echocardiography (DE) can identify the patients at risk, the location of the cardiac event is difficult to foresee because of the unpredictable plaque rupture of non-significant, vulnerable, coronary artery lesions. In the present study we matched preoperative assessed ischemic left ventricular (LV) territories using DE and intraoperatively observed new wall motion abnormalities (NWMA) using TEE to examine the chance of reproducibility of a NWMA at the same location preoperatively and intraoperatively as well. This matching correlation would be more emphasizing if perioperative NWMA were predictive of PO cardiac outcomes.

Materials and Methods

Study participants

In this prospective cohort study, patients over 40 years of age scheduled for non-cardiac vascular surgery at Erasmus University Medical Center, Rotterdam, the Netherlands, between June 2005 and September 2008 were candidates for inclusion in the study. Patients had to be scheduled for abdominal aortic aneurysm repair, abdominal aortic stenosis surgery or lower limb arterial reconstruction. We used the Lee's revised cardiac risk index which included history of ischemic heart disease, heart failure, cerebrovascular accidents, insulin therapy for diabetes mellitus and renal disease with serum creatinine > 2.0 mg/dL to abbreviate the cardiac risk factors, to identify patients at risk. [13] All patients underwent DE prior to surgery. Exclusion criteria for the study was the inability to retrieve adequate echocardiographic views pre or intraoperatively. After approval of the Medical Ethics Committee board and obtaining a patient informed consent, we included 54 consecutive adult patients.

Dobutamine echocardiography

All patients underwent DE to evaluate LV wall motion using dobutamine (± atropine) as a stressor. Two-dimensional echocardiography was performed at rest using Hewlett-Packard Sonos 1000 echo apparatus (*Hewlett-Packard*, Andover, MA, USA) with 2.5 and 3.5 MHz transducers. The technique yielded standard para-sternal and apical echocardiographic views under basal conditions and throughout graded dobutamine infusion. A stepwise incremental dose of dobutamine was administered, beginning at 10

μg/kg/min, increased by 10 μg/kg/min every 3 min until a definite end-point was attained. [14-16] During the dobutamine infusion, heart rate, blood pressure and electrocardiography were monitored. When the target heart rate (85% of maximum age and gender predicted heart rate) was not obtained at the maximum dobutamine dose (40 μg/kg/min), atropine (0.25-1.0 mg) was administered. [15, 17] Test end-points were achievement of target heart rate, maximal dose of dobutamine and atropine, extensive NWMA, >2mV downsloping ST-segment depression measured 80 ms after the J-point compared with the baseline, hypertension (blood pressure > 240/120 mmHg), a decrease in systolic blood pressure of > 40 mmHg compared with at rest, significant arrhythmias, or any intolerable adverse effects considered to be the result of dobutamine or atropine. An intravenous beta-blocker (metoprolol 1 to 5 mg) was available to reverse the adverse effects of dobutamine/atropine. The test was completed only after all ischemic regions had returned to baseline.

Transesophageal echocardiography

After induction of anesthesia and endotracheal intubation, the TEE probe was inserted. We based our TEE examination on the recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination. [18] The LV wall-motion was monitored in 6 views; namely; 3 mid-esophageal views (the 4-chamber mid-esophageal view, the mid-esophageal 2-chamber view, and the

mid-esophageal long-axis (LAX) view), and 3 trans-gastric views (basal, mid-papillary and apical trans-gastric views). Baseline images of the LV in short and long-axis were acquired and tape-recorded for offline analysis. The TEE probe depth and imaging planes of the basal views were noted to reproduce equivalent views intraoperatively. To improve the detection of intraoperative NWMA, we adopted a semi-continuous method keeping the TEE probe in the transgastric position with the mid-papillary left ventricular short-axis view continuously displayed and repeating the whole set of the examination views every 10 minutes and whenever there was echocardiographic suspicion of NWMA, hemodynamic change or surgical maneuver requiring special attention. For safety reasons, echocardiographic monitoring was freezed whenever the probe temperature exceeded 37.5°C which allowed the probe to cool down shortly.

TEE images were obtained using a standard adult 5 MHz multiplane transesophageal probe (GE LOGIQ 500 Probe, model H4552TB; General Electric) and the VingMed® System 5 echocardiographic imaging system (General Electric-VingMed Ultrasound, Horton, Norway). The main investigator was responsible for intraoperative image acquisition and passed a comprehensive training in transesophageal echocardiography in the study institute and performed 150 comprehensive TEE examinations as recommended by the American society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists. [18] The occurrences of LV NWMA, as well as the segmental location of each abnormality were recorded for each patient. The training

physicians (anesthesiologists and surgeons) were blinded to intraoperative echocardiographic findings except if significant NWMA (involving > 4 segments) necessitating immediate management were apparent on the screen.

Interpretation of echocardiographic views

DE test results and intraoperative TEE recordings were scored for rest WMA and new wall motion abnormalities (NWMA) using a 17-segment model as proposed by the American Society of Echocardiography and interpreted accordingly into a 7-wall LV model. [19-21] Transcription of LV segments to their LV wall involvement was done as shown in figure 1 redrawn based on the illustrations of LV wall in the TTE reports recommended by our institute and in the recommendation of the American society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists for the comprehensive TEE examination. [18]

A 5-point scale was used for wall motion analysis: 1 = normal; 2 = mild-moderate hypokinesis; 3= severely hypokinetic; 4 = akinesis; 5 = dyskinetic, as employed earlier. [14-17] Recorded echocardiographic loops were displayed simultaneously with resting images in a cine-loop format for interpretation. All images were analyzed at one time by two experienced readers blinded to clinical, electrocardiography, or other perioperative patient data. A NWMA was interpreted whenever a new or worsening regional LV motion was observed. Normal wall motion or an unchanged rest WMA were not considered for myocardial ischemia. Disagreements in interpretation were resolved by consensus.

Definition of end-points

All patients were monitored postoperatively for the development of adverse cardiac events. Standard electrocardiography and cardiac troponin-T (cTnT)) were serially measured after surgery on days 1, 3, 7, and 30 or at discharge. Tests were repeated when patients has had symptoms and/or signs of clinical myocardial ischemia. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The recommended lower limit of 0.03 ng/ml was used to define positive troponin T levels because lower levels do not meet the imprecision criteria of <10%.

The study end-point was the combination of elevated cTnT, MI, and cardiac death. Criteria of MI diagnosis included at least two of the following: cTnT ≥ 0.1 ng/ml, typical electrocardiographic changes (new Q waves >1 mm or >30 ms in electrocardiogram), and typical chest pain complaints. Cardiac death was defined as fatal MI (postmortem evidence of acute MI or definite criteria for MI within the 24 hr before death) and sudden cardiac death. Sudden cardiac death was defined as unexpected natural death due to cardiac causes, within one hour of the onset of acute symptoms.

Statistical Analysis

Categorical variables are expressed as percentages and were compared using the Pearson's chi-square test. Continuous variables are presented as mean (± SD) and were compared using the unpaired Student t-test. Correlation between DE and intraoperative TEE results in different LV locations was tested by means of kappa statistic (κ), to verify if a paired rest

WMA or NWMA locality, estimated by both techniques, might differ from agreement that could occur by chance alone. The κ measure of agreement between two observations ranges between 0 and 1 (0 is chance agreement, less than 0.4 poor agreement, 0.4 to 0.75 fair to good agreement, and over 0.75 excellent agreement). The measured κ value is presented in table or text.

For all tests, a P value <0.05 (two-sided) was considered significant. All analyses were performed using the syntax commands of SPSS® v15.0 statistical package for Windows® (SPSS Inc., Chicago, Illinois).

Results

Fifty-four consecutive patients were enrolled in the study. Preoperative baseline clinical characteristics are shown in table 1 including baseline echocardiographic variables. None of the examined patients had pacing devices. Operative characteristics are shown in table 2. We excluded six eligible patients from our study: two due to inability to insert the TEE probe which encountered resistance and four cases due to improper visualization of standard echo-views mentioned in the methods.

Dobutamine echocardiography and TEE showed rest WMA in 17 (31%) and 16 (30%) patients respectively, κ value on patient base = 0.92. The agreement for location of rest WMA was excellent, κ range = 0.77-1.0. Stress-induced NWMA during DE occurred in 17 patients (31%), whereas intraoperative NWMA were observed by TEE in 23 patients (43%), κ value on patient base = 0.65. However, the agreement for location of NWMA, using a

7-wall model was poor, κ range = 0.26-0.44. Echocardiographic locations of NWMA were presented in figure 2 and table 3. κ value for inter-observer variability for the different LV walls ranged between 0.91-0.98. A random sample of 10 patients were selected and re-scored for LV wall motion by each scoring investigator. Intra-observer κ value for the different LV walls ranged between 0.97-1.00.

During 30-day follow-up the composite endpoint occurred in 15 (28%) patients; cTnT release in 14 (26%), MI in 6 (11%), and cardiac death in 3 (6%); (Table 4). In these 15 patients, 10 (67%) experienced both pre and intraoperative NWMA, while in 4 (27%) only intraoperative NWMA were observed. In only one patient (7%) without pre- and intraoperative NWMA, troponin release was observed. This patient did not experience ischemic symptoms or electrocardiographic abnormalities. The relation of preoperative and intraoperative NWMA and PO outcome is presented in table 4. In all 6 patients who experienced a PO MI, the location of electrocardiographic changes matched with the intraoperatively observed NWMA by TEE, while in 2 (33%) there was an agreement with the preoperative induced ischemia during DE.

Figure 3 represented the sub-division of the total population according to preoperative and intraoperative development of NWMA and PO cardiac outcome. The presence of multi-vessel CAD as detected by DE and intraoperatively by TEE was in favor of a composite outcome ($P < 0.05$ for DE and $P = 0.001$ for intraoperative TEE) but not a single-vessel disease

(P=NS). In table 5, we presented the calculated diagnostic indices of both preoperative DE and intraoperative TEE for the study outcomes.

Discussion

In this study we used echocardiography to observe the location of NWMA induced preoperatively during DE and those developed intraoperatively by TEE monitoring in 54 high-risk vascular surgical patients. Using the κ coefficient, we observed an excellent correlation between preoperative and intraoperative rest WMA (κ range 0.8-1.0), indicating concordance between preoperative and intraoperative echocardiographic recordings. However poor agreement correlations were found between preoperative and intraoperative locations of NWMA ($\kappa \leq 0.4$).

While patients with severe and unstable coronary disease are warranted to undergo preoperative stress testing to direct toward the optimal prophylactic strategy, those who have stable coronary disease do not show much benefit from stress testing over clinical stratification. Dobutamine echocardiography; among other stress tests; accurately determine reversible ischemic regions. However, those tests have stronger negative than positive predictive power particularly in the stable coronary disease population. Perioperative beta-blockade had proven to be a sufficient prophylactic regime in such patients. In the present investigation, approximately 45% of our population presented with established coronary artery disease, 14% presented with two and 43% showed three or more risk factors among the Lee's revised cardiac risk index with fair LV function in average estimated by

mean ejection fraction. This stratification puts this population in the grey zone of where optimized medical therapy is weighed against coronary revascularization. The purpose of this study was to determine which of the two prophylactic measures is optimal in order to provide better PO cardiac outcome. [22, 23]

Autopsy studies had shown the pathologic similarity of perioperative MI to that occurring in the non-operative setting, however, they were unsuccessful at the predictability of the site of vulnerable plaque rupture in most instances of perioperative MI based on the severity of coronary stenosis. [6, 7] This means that selective targeting of isolated culprit plaque(s) by means of a focused revascularization techniques, as a prophylactic measure cannot be employed with adequate results.

Due to the high propensity of CAD in the peripheral arterial disease population requiring elective surgical intervention, preoperative cardiac evaluation might suggest an indication for coronary revascularization in those presenting with severe coronary stenosis. [5, 24, 25] Pooled data from previous studies were not favor of preoperative coronary revascularization prior to major non-cardiac surgery. In the CARP trial, coronary arterial revascularization in 258 symptomatically stable; but severe CAD patients did not confer beneficial outcomes on perioperative or long-term than in the control group (252 patients) prior to major vascular operations. [3] Similar findings were shown in the DECREASE-V randomized pilot study in 101 high-risk vascular surgical patients randomized either to no intervention (n=52) or coronary revascularization before vascular surgery (n=49). [26] The CASS trial

investigators suggested similar conclusions, when equivocal long-term outcomes were observed between coronary artery bypass graft surgery and intensive medical treatment patient groups. [27] These findings remained the same after 10 years of follow-up. Comparable results were shown by medical treatment, surgical treatment, or PCI. [28] Finally, reports of unwanted outcomes had been addressed for PCI prior to non-cardiac surgery in the at-risk CAD population. [29, 30] Indeed, the reason that coronary artery bypass graft was found superior to PCI prior to vascular surgery in one study was the more extensive revascularization in the coronary artery bypass graft group. [31]

We reported PO cardiac outcomes as 26%, 11% and 6% for PO cTnT release, MI and cardiac death respectively. These events were predictable by the induction of NWMA by a DE stress test and even better predicted by the occurrence of intraoperative NWMA. In our population, NWMA induced during DE or detected intraoperatively by TEE presented more with multi-vessel CAD form, which was also correlated with the combined cardiac outcome (P=0.003 for multi-vessel reversible ischemia by preoperative DE, and P=0.001 for multi-vessel reversible ischemia by intraoperative TEE) but not a single coronary vessel' related NWMA (P=NS). This indicated the more extensive nature of coronary vascular disease they had.

We found perfect matching of intraoperative NWMA location with PO electrocardiographic locality of MI indicating the accumulation of most perioperative stressors on the vulnerable myocardium of the vascular surgical patient in the intraoperative phase exhausting the moribund coronary

reserve around the end of surgery which would hence yield most fatal MI's in the immediate PO phase up to 12 hours PO. This coincides with the well-established knowledge that > 50% of perioperative MI's do occur in the immediate PO period and led to recommending twice daily electrocardiography in the first PO day. Additionally, we reported PO cTnT release in 14 patients (26%). In 8 (57%) of them, troponin release was not associated with MI. LeManach and colleagues found earlier in a larger cohort of vascular surgical patients that PO abnormal troponin (14% of 1136 patient population). Elevated cardiac troponins were related to PO MI (in 35% of the elevated troponin patients) in two distinct fashions (early and late) indicating two different sets of myocardial stressors nearer and later from the end of surgery. [32] Our incidence of elevated PO troponin is similar to or even reduced to that reported in other research in similar populations. [25, 33, 34] Silent myocardial ischemic events would result from the effects of perioperative stressors in a myocardial demand/supply mismatch insufficient to progress to evident myocardial damage. This is supported by the finding that perioperative cTnT is related to poor long-term cardiac outcomes. This would explain the higher rates of sub-clinical ischemic events (elevated cTnT or transient NWMA) over harder cardiac events in our and other populations. [23, 25, 35]

Intraoperative TEE showed an additional incremental value on the prediction of PO cardiac events. Both preoperative NWMA during DE and intraoperative NWMA detected by TEE had a significant association with the

composite cardiac outcome ($P < 0.001$). No events of cardiac death or PO MI occurred in patients without intraoperative NWMA.

Study limitation

We had several limitations in the present study. Some cases were excluded for either technical difficulty in image acquisition at any stage or inappropriate views to judge LV wall motion. We could not continue to enroll more patients for time factors limiting the level of power of our significant results especially those related to the regression analysis. Some NWMA were probably missed particularly prior to probe insertion following the start of anesthesia induction. Coronary angiography was not clinically indicated preoperatively in the studied patients and hence we could not relate our findings to the more pathognomonic angiographic data. Some reversible segmental LV wall motion abnormalities could have been missed in some views while obtaining others for offline analysis. Nevertheless, concomitant mechanical effects like tethering by a coexisting myocardial scarring or ballooning effect during aortic cross-clamping would have influenced our judgment for a NWMA. Finally, Kappa measurement is a useful statistic to look for the chance of agreement between two sets of readings. However, it has some flaws particularly its vulnerability towards difference in prevalence regardless a fixed specificity and sensitivity between the two readings particularly when sophisticated variables and heterogenous examination groups are used. [36, 37]

Conclusion

In patients undergoing major vascular surgery, preoperative dobutamine echocardiography and intraoperative transesophageal echocardiographic monitoring of wall motion changes had good correlation with PO cardiac troponin-T release and myocardial infarction. Transesophageal echocardiography; however; had a stronger association with all PO cardiac events. Reproducibility of wall motion abnormalities in the same myocardial wall locations at different perioperative times was not achievable. This suggests the superiority of optimized medical therapies over the invasive interventions focused on particular culprit lesions for the prophylaxis against perioperative myocardial ischemia. In our population receiving beta-blocking medications, the higher predictive power of intraoperative TEE over preoperative DE for PO outcomes further emphasizes the importance of optimized medical treatments over preoperative cardiac testing in fairly stable coronary disease populations.

References

1- Mackey WC, Fleisher LA, Haider S, Sheikh S, Cappelleri JC, Lee WC, Wang Q, Stephens JM: Perioperative myocardial ischemic injury in high-risk vascular surgery patients: Incidence and clinical significance in a prospective clinical trial. J Vasc Surg. 2006; 43: 533-8.

2- Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D: Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol 1999; 19: 538-45.

3- McFalls EO, ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG: Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004; 351: 2795-804.

4- Sautter RD, Myers WO, Ray JF 3rd, Wenzel FJ.: Relationship of fibrinolytic system to postoperative thrombotic phenomena. Arch Surg 1973; 107: 292–6.

5- Ellis SG, Hertzer NR, Young JR, Brener S: Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol 1996; 77: 1126–8.

6- Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA: Pathology of fatal perioperative myocardial infarction: Implications regarding pathophysiology and prevention. Int J Cardiol 1996; 57: 37–44.

7- Cohen MC, Aretz TH: Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999; 8: 133–9.

8- Gewertz BL, Kremser PC, Zarins CK, Smith JS, Ellis JE, Feinstein SB, Roizen MF: Transesophageal echocardiographic monitoring of myocardial ischemia during vascular surgery. J Vasc Surg 1987; 5: 607-13.

9- London MJ, Tubau JF, Wong MG, Layug E, Hollenberg M, Krupski WC, Rapp JH, Browner WS, Mangano DT: The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. S.P.I. Research Group. Anesthesiology 1990;73:644-55.

10- Koolen JJ, Visser CA, Reichert SL, Jaarsma WJ, Kromhout JG, van Wezel HB, Dunning AJ: Improved monitoring of myocardial ischaemia during major vascular surgery using transoesophageal echocardiography. Eur Heart J 1992;13:1028-33.

11- Mangano DT, London MJ, Tubau JF, Browner WS, Hollenberg M, Krupski W, Layug EL, Massie B: Dipyridamole thallium-201 scintigraphy as a

preoperative screening test. A reexamination of its predictive potential. Study of Perioperative Ischemia Research Group. Circulation 1991; 84: 493-502.

12- Watters TA, Botvinick EH, Dae MW, Cahalan M, Urbanowicz J, Benefiel DJ, Schiller NB, Goldstone G, Reilly L, Stoney RJ: Comparison of the findings on preoperative dipyridamole perfusion scintigraphy and intraoperative transesophageal echocardiography: Implications regarding the identification of myocardium at ischemic risk. J Am Coll Cardiol 1991; 18:93-100.

13- Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100: 1043–9.

14- Thatipelli MR, Pellikka PA, McBane RD, Rooke TW, Rosales GA, Hodge D, Herges RM, Wysokinski WE: Prognostic value of ankle-brachial index and dobutamine stress echocardiography for cardiovascular morbidity and all-cause mortality in patients with peripheral arterial disease. J Vasc Surg 2007; 46: 62-70.

15- Poldermans D, Fioretti PM, Forster T, Boersma E, Arnese M, du Bois NA, Roelandt JR, van Urk H: Dobutamine-atropine stress echocardiography for assessment of perioperative and late cardiac risk in patients undergoing major vascular surgery. Eur J Vasc Surg. 1994 ;8: 286-93.

16- Bax JJ, Poldermans D, Elhendy A, Cornel JH, Boersma E, Rambaldi R, Roelandt JR, Fioretti PM: Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. J Am Coll Cardiol. 1999; 34: 163-9.

17- Poldermans D, Arnese M, Fioretti PM, Salustri A, Boersma E, Thomson IR, Roelandt JR, van Urk H: Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol 1995; 26: 648 –53.

18- Shanewise JS, Cheung AT, Aronson S, Stewart WJ, Weiss RL, Mark JB, Savage RM, Sears-Rogan P, Mathew JP, Quiñones MA, Cahalan MK, Savino JS: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. Anesth Analg. 1999; 89: 870-84.

19- Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, et al.: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards,

Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989; 2: 358-67.

20- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. J Am Soc Echocardiogr. 2005; 18: 1440-63.

21- Bayés de Luna A, Wagner G, Birnbaum Y, Nikus K, Fiol M, Gorgels A, Cinca J, Clemmensen PM, Pahlm O, Sclarovsky S, Stern S, Wellens H, Zareba W; International Society for Holter and Noninvasive Electrocardiography: A new terminology for left ventricular walls and location of myocardial infarcts that present Q wave based on the standard of cardiac magnetic resonance imaging: A statement for healthcare professionals from a committee appointed by the International Society for Holter and Noninvasive Electrocardiography. Circulation. 2006; 114: 1755-60.

22- Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: Focused update on perioperative beta-blocker therapy--a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Anesth Analg. 2007; 104: 15-26.

23- Parent MC, Rinfret S. The unresolved issues with risk stratification and management of patients with coronary artery disease undergoing major vascular surgery. Can J Anaesth. 2008; 55: 542-56.

24- Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF 3rd, Graor RA, Dewolfe VG, Maljovec LC: Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg. 1984; 199: 223-33.

25- Feringa HH, Karagiannis SE, Vidakovic R, Elhendy A, ten Cate FJ, Noordzij PG, van Domburg RT, Bax JJ, Poldermans D: The prevalence and prognosis of unrecognized myocardial infarction and silent myocardial ischemia in patients undergoing major vascular surgery. Coron Artery Dis. 2007; 18: 571-6.

26- Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrün M, de Jaegere P, Maat A, van Sambeek MR, Kertai MD, Boersma E; DECREASE Study Group: A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: The DECREASE-V Pilot Study. J Am Coll Cardiol. 2007; 49: 1763-9.

27- Coronary artery surgery study (CASS): A randomized trial of coronary artery bypass surgery. Survival data. Circulation 1983; 68: 939-50.

28- Espinola-Klein C, Rupprecht HJ, Erbel R, Nafe B, Brennecke R, Meyer J: Ten-year outcome after coronary angioplasty in patients with single-vessel coronary artery disease and comparison with the results of the Coronary Artery Surgery Study (CASS). Am J Cardiol. 2000; 85: 321-6.

29- Kałuza GL, Joseph J, Lee JR, Raizner ME, Raizner AE: Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol. 2000; 35: 1288-94.

30- Posner KL, Van Norman GA, Chan V: Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. Anesth Analg. 1999 ; 89: 553-60.

31- Ward HB, Kelly RF, Thottapurathu L, Moritz TE, Larsen GC, Pierpont G, Santilli S, Goldman S, Krupski WC, Littooy F, Reda DJ, McFalls EO: Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of perioperative myocardial infarctions during subsequent vascular surgery. Ann Thorac Surg. 2006; 82: 795-800.

32- Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B: Early and delayed myocardial infarction after abdominal aortic surgery. Anesthesiology. 2005; 102: 885-91.

33- Feringa HH, Karagiannis S, Vidakovic R, Noordzij PG, Brugts JJ, Schouten O, van Sambeek MR, Bax JJ, Poldermans D: Comparison of the incidences of cardiac arrhythmias, myocardial ischemia, and cardiac events in patients treated with endovascular versus open surgical repair of abdominal aortic aneurysms. Am J Cardiol. 2007; 100: 1479-84.

34- Bottiger BW, Snyder-Ramos SA, Lapp W, Motsch J, Aulmann M, Schweizer M, Layug EL, Martin E, Mangano DT; The investigators of the Multicenter Study of Perioperative Ischemia (MCSPI) Research Group, Inc. and the Ischemia Research and Education Foundation: Association between

early postoperative coagulation activation and peri-operative myocardial ischaemia in patients undergoing vascular surgery. Anaesthesia. 2005; 60: 1162-7.

35- Smith JS, Cahalan MK, Benefiel DJ, Byrd BF, Lurz FW, Shapiro WA, Roizen MF, Bouchard A, Schiller NB: Intraoperative detection of myocardial ischemia in high-risk patients: Electrocardiography versus two-dimensional transesophageal echocardiography. Circulation. 1985; 72: 1015-21.

36- Maclure M, Willett WC. Misinterpretation and misuse of the kappa statistic. Am J Epidemiol. 1987; 126: 161-9.

37- Tooth LR, Ottenbacher KJ. The kappa statistic in rehabilitation research: An examination. Arch Phys Med Rehabil. 2004; 85: 1371-6.

Figures

Fig. 1. Left ventricular (LV) myocardial segmentation for echocardiographic wall motion analysis with corresponding distribution of coronary arterial blood supply, showing segmental distribution of the seven LV walls in dobutamine echocardiography (A) and in transesophageal echocardiography (B). Cx = circumflex artery; LAD = left anterior descending coronary artery; RCA = right coronary artery.

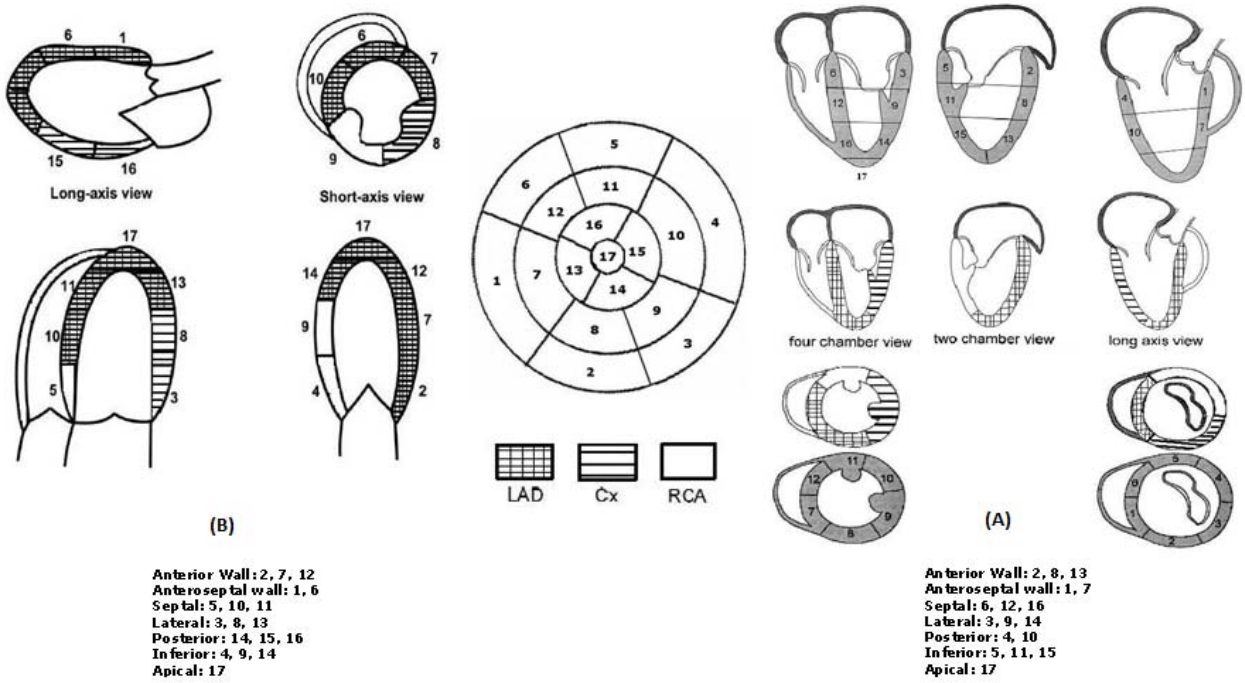


Fig. 2. Agreement for location in ischemic left ventricular (LV) walls between preoperative and intraoperative echocardiographies.

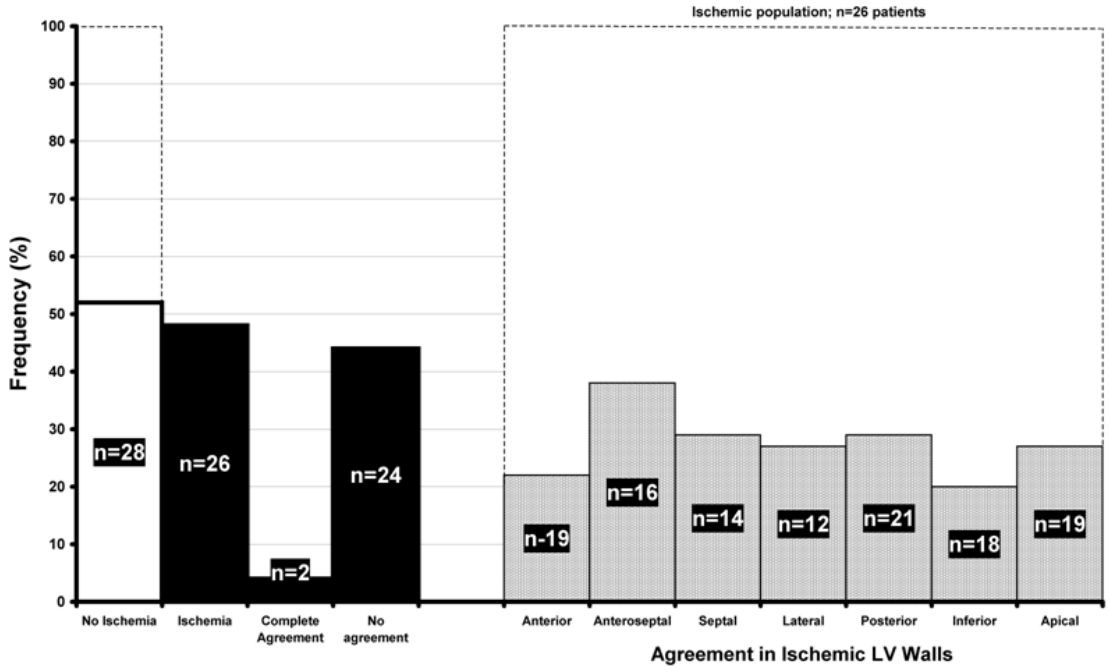
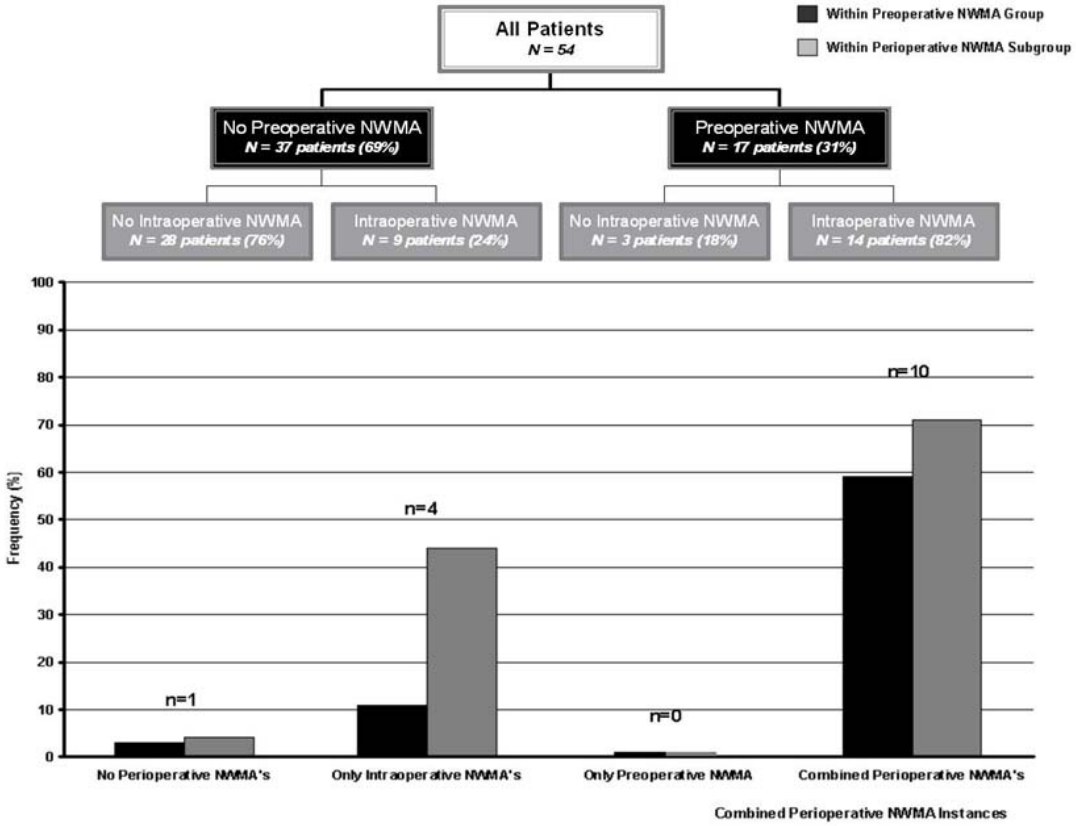


Fig. 3. Composite cardiac outcome according to perioperative new wall motion abnormalities (NWMA).



Tables

Table 1. Baseline and Perioperative Patient Characteristics in All and Sub-populations Based on the Acquisition of A Perioperative NWMA.

	All Patients	Preoperative DSE			Intraoperative TEE		
		NWMA	No NWMA	P value	NWMA	No	P value
	N=54	N=17 (31)	N=37 (69)		N=23 (43)	N=31 (57)	
Patient Demographics:							
Mean age (± SD)	65.5±12.1	69.7±12.1	63.6±11.7	NS	71.0±11.9	61.4±10.7	< 0.05
Male sex	48 (89)	15 (88)	33 (89)	NS	20 (87)	28 (90)	NS
Angina pectoris	13 (24)	6 (46)	7 (54)	NS	10 (44)	3 (10)	NS
Previous myocardial infarction	24 (44)	10 (59)	14 (38)	NS	14 (61)	10 (32)	< 0.05
Previous coronary revascularization €	14 (26)	6 (43)	7 (57)	NS	7 (30)	7 (23)	NS
Previous stroke	11 (20)	5 (29)	6 (16)	NS	7 (30)	4 (13)	NS
Diabetes mellitus £	12 (22)	8 (47)	4 (11)	< 0.05	6 (26)	6 (19)	NS
Renal dysfunction Ω	8 (15)	5 (29)	3 (8)	< 0.05	6 (26)	2 (7)	< 0.05
Hypertension ¥	34 (63)	11 (65)	23 (62)	NS	15 (65)	19 (61)	NS
Hypercholesterolemia	29 (54)	13 (77)	16 (43)	< 0.05	15 (65)	14 (45)	NS
Chronic obstructive pulmonary disease	22 (41)	8 (47)	14 (38)	NS	13 (57)	9 (29)	< 0.05
Congestive heart failure	3 (6)	0 (0)	3 (8)	NS	3 (13)	0 (0)	< 0.05
Echocardiographic features§							
Left ventricular hypertrophy	23 (43)	9 (53)	14 (38)	NS	14 (61)	9 (29)	NS
Ejection Fraction (mean ± SD)	47.1±8.6	44.8±9.6	47.7±6.5	NS	44.9±5.8	44.7±5.2	NS
Fractional Area Change (mean ± SD)	43.9±8.2	44.3±7.9	43.3±8.3	NS	45.0±8.8	43.1±8.1	NS
Fraction Shortening (mean ± SD)	26.9±5.2	25.2±5.1	28.4±5.0	NS	25.9±3.6	27.4±5.8	NS
ASA Physical Status classification:							
● ASA Class I	3 (6)	0 (0)	3 (8)	NS	0 (0)	3 (10)	NS
● ASA Class II	13 (24)	4 (24)	9 (24)	NS	5 (22)	8 (26)	NS
● ASA Class III	29 (54)	8 (47)	21 (57)	NS	12 (52)	17 (55)	NS
● ASA Class IV	9 (17)	5 (29)	4 (11)	NS	6 (26)	3 (10)	NS
LEE RCRI:							
● I	17 (32)	0 (0)	17 (46)	0.001	2 (9)	15 (48)	< 0.05
● II	14 (26)	3 (18)	11 (30)	NS	6 (26)	8 (26)	NS
● ≥ III	23 (43)	14 (61)	9 (39)	< 0.001	15 (65)	8 (26)	< 0.01
Medication:							
Beta-blockers	54 (100)	17 (100)	37 (100)	NS	23 (100)	31 (100)	NS

Statins	29 (54)	14 (82)	15 (41)	< 0.05	16 (70)	13 (42)	< 0.05
ACE-inhibitors	13 (24)	7 (41)	6 (16)	< 0.05	9 (39)	4 (13)	< 0.05
Calcium-channel blockers	9 (17)	6 (35)	3 (8)	< 0.05	6 (26)	3 (10)	NS
Aspirin	35 (65)	11 (65)	24 (65)	NS	14 (61)	21 (68)	NS
Nitrates	2 (4)	1 (6)	1 (3)	NS	2 (9)	0 (0)	NS
Diuretics	12 (22)	5 (29)	7 (19)	NS	8 (35)	4 (13)	NS

Continuous variables are shown as mean (SD), while dichotomous variables are shown as number (% of column totals).

€ Coronary artery bypass graft surgery and/or percutaneous coronary intervention procedures.

£ Fasting blood sugar ≥ 7 mmol/L or use of hypoglycemic agents.

Ω Serum creatinine level ≥ 2.0 mg/dl [177 mmol/L] or requirement of dialysis.

¥ Arterial blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs.

Abbreviations:- ASA: American Society of Anesthesiologists, LEE RCRI: Lee's Revised Cardiac Risk Index.

Table 2. Population Operative Characteristics with respect to the distribution of hemodynamic covariates on the Acquisition of A Perioperative NWMA.

	All Patients N=54	Intraoperative TEE NWMA N=23 (43)	Intraoperative TEE No NWMA N=31 (57)	P value
Anesthetic technique:				
General anesthetic	31 (57%)	10 (44%)	21 (68%)	NS
Combined general and epidural anesthesia	23 (43%)	13 (57%)	10 (32%)	NS
				NS
Surgical procedure:				
● Open aortic prosthetic repair	34 (63%)	17 (74%)	17 (55%)	NS
- Clamping duration (min)	49.4±54.6	52.4±45.1	47.9±55.7	NS
● LLR	20 (38%)	6 (26%)	14 (45%)	NS
● Procedure duration (min) €	267.6±72.1	275.1±45.4	264.6±64.1	NS
● Operative blood loss (L) €	0.5 (0.6-1.9)	0.6 (0.2-1.9)	0.5 (0.4-1.8)	NS
Intraoperative fluid administration				
● Crystalloids (L) €	4.0 ± 0.2	4.6±2.9	3.8±1.9	NS
● Colloids (L) €	1.5±0.8	1.6±0.8	1.4±0.7	NS
● Packed cells (units) €	4.3±1.5	3.8±1.8	4.5±1.2	NS
● Plasma (units) €	3.0±1.0	2.5±1.1	3.1±0.8	NS
● Cell-saver blood £	0.4 (0.3-1.2)	0.4 (0.2-1.0)	0.6 (0.3-1.4)	NS
Hemodynamic variables				
Heart Rate €	67.1±11.9	69.6±11.5	66.5±7.7	NS
Mean Arterial Pressure €	77.7±13.4	80.5±11.5	73.2±15.4	NS
Intraoperative urine output (L) £	0.5 (0.4-0.7)	0.7(0.5-0.8)	0.6 (0.4-0.7)	NS

Continuous variables are shown as mean ± standard deviation (€) or mean ± interquartile range (£), while dichotomous variables are shown as number (% of column totals).

Abbreviations:- LLR: lower extremity arterial revascularizations, NWMA: New wall motion abnormalities, TEE: Transesophageal echocardiography. Abbreviated units of measurement provided; (L): Liter and (min): minute.

Table 3. Agreement for the association and locality distribution of resting "(a)" and ischemic "(b)" LV walls presenting with WMA's in preoperative DSE and intraoperative TEE.

(a) Pre-recording variables (at rest)			
	DE N (%)	**TEE N (%)**	***K***
Patients with Rest WMA	17 (31)	16 (30)	0.917
**** Locality of the Rest WMA:***			
• Anterior Wall	7 (41)	9 (56)	0.821
• Antero-septal Wall	10 (59)	12 (75)	0.843
• Septal Wall	11 (65)	11 (69)	1.0
• Lateral Wall	7 (41)	9 (56)	0.821
• Posterior Wall	7 (41)	7 (44)	1.0
• Inferior wall	9 (53)	9 (56)	1.0
• Apical	13 (76)	10 (63)	0.769
(b) Preoperative ischemia during DSE and intraoperative ischemia by TEE			
	DE N (%)	**TEE N (%)**	***K***
Patients with NWMA	17 (31)	23 (89)	0.653
**** Locality of the NWMA:***			
• Anterior Wall	5 (29)	6 (26)	0.292
• Antero-septal Wall	8 (47)	14 (61)	0.440
• Septal Wall	9 (53)	13 (57)	0.321
• Lateral Wall	5 (29)	9 (39)	0.351
• Posterior Wall	4 (24)	5 (22)	0.260
• Inferior Wall	4 (24)	8 (35)	0.395
• Apical	9 (53)	4 (17)	0.351
Single vessel reversible ischemia	7 (41)	8 (35)	0.233
Multi-vessel reversible ischemia	10 (69)	15 (65)	0.336

Abbreviations:- DE: dobutamine echocardiography, ***K*** : Kappa measurement value, **NWMA:** New wall motion abnormalities, **TEE:** Transesophageal echocardiography, **WMA:** Wall motion abnormalities.

Table 4. Postoperative Patient Outcomes According to Ischemia Wall Agreement Between Preoperative and Intraoperative NWMA.

	All Patients	Preoperative DE			Intraoperative TEE		
	N=54	NWMA N=17 (31)	No NWMA N=37 (69)	P value	NWMA N=23 (43)	No NWMA N=31 (57)	P value
Postoperative Outcomes:							
PO cTnT release	14 (26)	9 (53)	5 (14)	< 0.05	13 (57)	1 (3)	< 0.001
PO MI	6 (11)	6 (35)	0 (0)	< 0.001	6 (26)	0 (0)	< 0.05
Cardiac Death	3 (6)	2 (12)	1 (3)	NS	3 (13)	0 (0)	< 0.05
Composite outcome	15 (28)	10 (59)	5 (14)	0.001	14 (61)	1 (3)	< 0.001

Abbreviations:- DE: dobutamine echocardiography, **NWMA:** New wall motion abnormalities, **PO cTnT:** Postoperative cardiac troponin-T, **PO MI:** Postoperative myocardial infarction, **TEE:** Transesophageal echocardiography.

Table 5. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of preoperative dobutamine echocardiography (DE) and intraoperative transesophageal echocardiography (TEE) for the study outcomes.

Positive Predictive Value					
Echocardiographic Technique	**Intraoperative NWMA**	**PO cTnT**	**PO MI**	**Cardiac death**	**Composite endpoint**
DE	61%	64%	100%	67%	67%
TEE	-	93%	100%	100%	93%

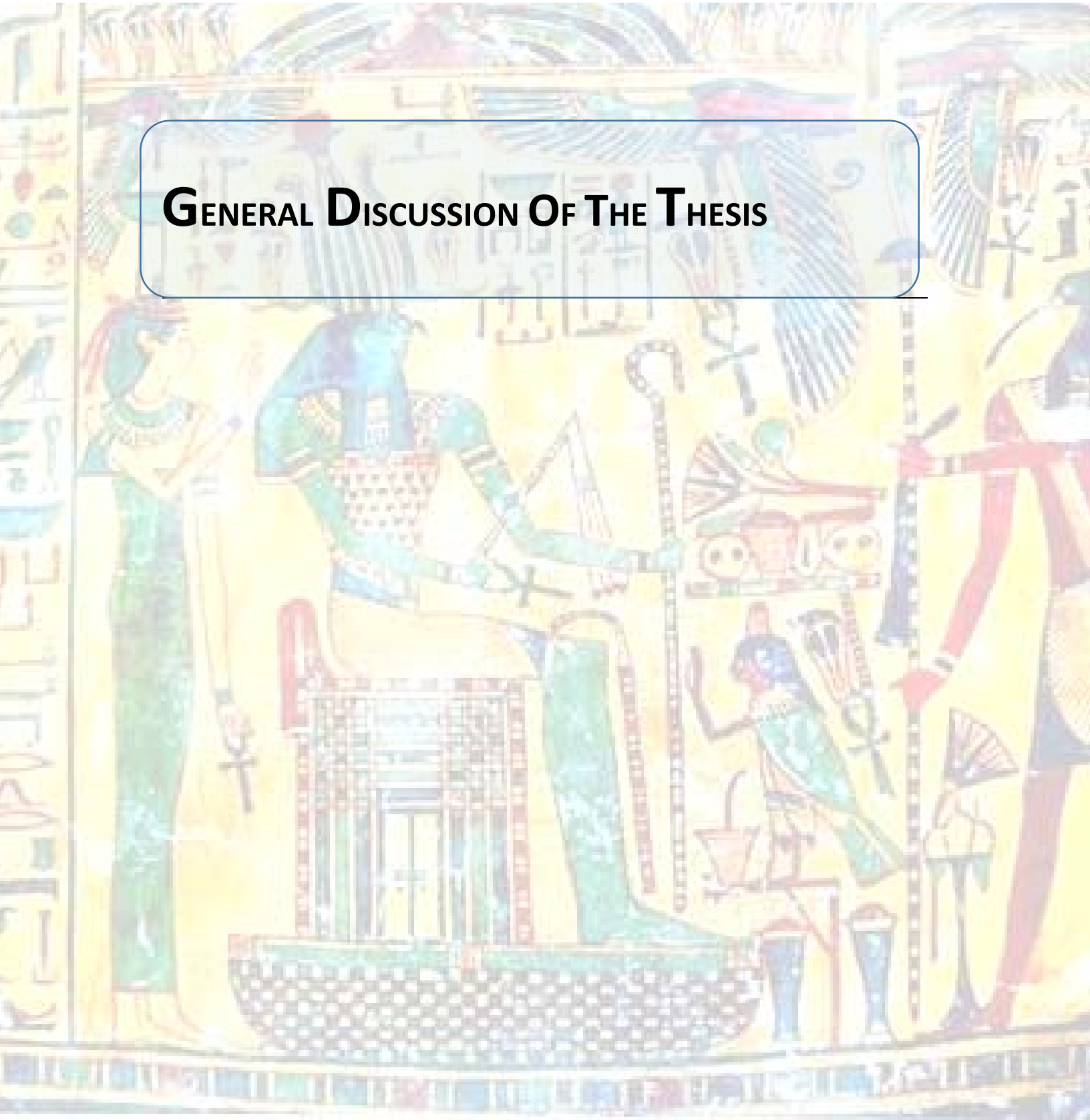
Negative Predictive Value					
Echocardiographic Technique	**Intraoperative NWMA**	**PO cTnT**	**PO MI**	**Cardiac death**	**Composite endpoint**
DE	90%	80%	77%	71%	82%
TEE	-	75%	65%	61%	77%

Sensitivity					
Echocardiographic Technique	**Intraoperative NWMA**	**PO cTnT**	**PO MI**	**Cardiac death**	**Composite endpoint**
DE	**82%**	53%	35%	12%	59%
TEE	-	57%	26%	13%	61%

Specificity					
Echocardiographic Technique	**Intraoperative NWMA**	**PO cTnT**	**PO MI**	**Cardiac death**	**Composite endpoint**
DE	76%	87%	100%	97%	87%
TEE	**-**	97%	100%	100%	97%

Abbreviations:- DE: dobutamine echocardiography, **NWMA:** New wall motion abnormalities, **PO cTnT:** Postoperative cardiac troponin-T**, PO MI:** Postoperative myocardial infarction, **PPV:** positive predictive value, **NPV:** Negative predictive value, **TEE:** Transesophageal echocardiography.

General Discussion Of The Thesis



General Discussion of this Thesis

This thesis consists of two sections: one linking preoperative patient bodily composition status (termed as body mass index) to long-term outcomes and the other links preoperative and intraoperative echocardiographic testing to major postoperative (cardiac) complications. In view of the first part, one can say that a reflective image of expected outcome can be related to a patient's original body mass when presenting prior to a surgical intervention. As the association between preoperative factors and mortality were not uncommon to nowadays health risk stratification and prognosis, a simple reaction would be a logic intervention to influence these outcomes by measures of prevention. Nevertheless, the unexpected risk association within our research between BMI and mortality witnessed a long debate in the medical community. This unexpected finding would be "conditionally" expressed as the changing relationship between body mass index and mortality. In addition, our data represent the first published studies to report an inverse relationship between body mass index and mortality in patients suffering from peripheral arterial disease, polyvascular disease, and coronary artery disease in particular and the general surgery population in general. Our studies are observational in nature following the essential belief that observation was the founder of all science.

Cardiovascular complications remain a major concern in vascular surgical patients who present with propensity of cardiac risk factors. [1,2] The association of peripheral vascular disease with coronary artery disease is also known to affect chances of survival. [3] Projection of perioperative patient risk estimates to long-term adverse events is becoming more and more of clinical importance. Overweight and obesity are among factors researched. By advancements in early detection and correction of major known life-threatening conditions and prosperity of modern nutrition, our modern societies became involved in two significant epidemiologic phenomena: ageing and obesity. [4-7]

Part I: The Obesity Paradox in the Surgical Population

As a conclusion form this part, BMI definitely showed an altered relationship with mortality in our populations of peripheral arterial disease patients; where survival was found to be proportionally related to weight. However, one should be cautious to generalize conclusions of our studies. First of all, our populations represented relatively older individuals with a mean age above 58 (i.e. average old patients). Secondly, these patients represent a medically-targeted population with moderate to severe burden of associated co-morbidities. A survival advantage of BMI was shown in the overweight and moderate obesity, whereas being underweight always showed worsened survival. The relationship was shown for both short-term and long-term mortality (i.e. in chapter 3, we found this relationship [partially] true in overweight patients for short-term mortality within 30-days postoperatively). The influence of severe COPD, and cancer-related mortality correlated with the survival disadvantage observed in underweight patients (chapters 2 & 3), whereas higher incidence of cardiovascular death was observed in both the underweight and the severely obese.

Our series of studies joined an ongoing debate in the medical literature regarding the apparent conflict between this observation and the common and acknowledged perception about the health-related risks of obesity. Consequently, a careful interpretation of research findings might guide us towards a better understanding of this phenomenon and its implication in today's apparently, more complicated physician's thoughts. This means simply that considerations for interventions to reduce weight on BMI in different "health and disease states" need further medical thought and guidelines. Importantly, our studies are observational in design using retrospective data.

Would differentiation of causes of death partially explains the paradox?

The average body mass is increasing by around 0.4% yearly in the Western population. [8] Meanwhile, the life expectancy in Western societies could be interpreted as a proof for success in adopting extensive primary care regimes to prevent and early manage major diseases and risk factors such as hypertension, diabetes, coronary artery disease, stroke and COPD. However, smoking, alcohol consumption and cancer occurrence remain little influenced. BMI is known for a preferential incidence of certain types of cancer such as colo-rectal, breast and ovarian cancers in obesity, while being underweight is known for others such as lung and gastric cancers. Therefore, to avoid biasing our knowledge from studies on populations with particular cancer-types, these studies were not taken into consideration during this discussion. We claim that at least three specific causes of mortality are responsible for explaining the BMI paradox based on our examined populations; i.e. cardiovascular mortality (Chapter 1), respiratory causes (chapter 2) and cancer (Chapter 3). In a study

of re-vascularized coronary artery disease patients, underweight patients were susceptible for cardiovascular death and myocardial infarction, whereas overweight patients had low affinity to acquire cardiovascular death. [9] In an analysis of cause-specific mortality in a pooled population from different stages of the National Health and Nutrition Examination Surveys (NANHES) involving 571,042 person-years of follow-up, underweight was associated with increased mortality from non-cancer, non-cardio-vascular causes. Overweight was associated with decreased mortality from non-cancer, non-cardiovascular causes. Obesity was associated with significantly increased cardiovascular mortality. When the authors repeated the analysis for overweight and obesity combined, these were found to be associated with increased mortality from diabetes and kidney disease, and decreased mortality from other non-cancer, non-cardio-vascular causes. Obesity was associated with increased mortality from cancers considered obesity-related, but not from other cancers. [10] We tested the assumption that the general surgical population risk of cancer death can influence the altered relation between BMI and long-term mortality. We found significantly higher cancer-death rates among the underweight, while higher BMI categories showed lower mortality from cancer when compared to normal weight subjects. The association between cerebro-cardiovascular mortality and either BMI category remained inconclusive. In a census-linked Swiss national cohort of 31,578 individuals aged 25-74 years, excessive mortality in the underweight category was linked to external; non-cardiovascular, non-cancer, non-respiratory causes. [11] Underweight smokers have triple hazard of mortality as compared to underweight non-smokers.

Ageing as a cachectic process and introducing the concept of the critical body mass

Parallel to the epidemic of obesity, ageing became a global epidemiologic feature. Ageing is essentially a cachectic stage of human biology characterized by decreased caloric intake, increased catabolism, sedentary life-style and decreased activity. [12, 13] Decreased body mass with advancing age is due to both sarcopenia and decreased fat mass. Decreased fat mass would deplete energy stores, prodromal to lean body mass loss and increase inflammation, while sarcopenia causes frailty. [14, 15] It is thought that increased leptin secretion from white adipocytes plays a major mediator of these metabolic effects. [16, 17] As fat loss occurs first, followed by muscle protein catabolism, we would suggest a concept of critical body mass entailing the percentage of total body weight (or BMI) loss prior to the point at which muscle breakdown ensues. It has been suggested; in cancer patients receiving chemotherapy, that this critical point is 5% from the original BMI. [18, 19] The higher the initial BMI, the wider would be this critical gap and the more stable would be the status of the patient's metabolism. Moreover, there is an evidence that ageing associated with overweight and/or early obesity with re-distribution of fat cells in favor of the subcutaneous fat implicates a state of leptin resistance slowing down the sarcopenia of old age. [20] That was expressed in a recent editorial

commenting on the new survival advantage of increased body mass as: "*Is the 40 the new 30?*" [21] We would raise this idea as "*would 65 years with BMI of 40, equal the new 50 years of age*?"

BMI single measurement or a process of changing weight?

Another dynamic aspect of BMI is its probability for change along the individual's life-time. The frailty of ageing is probably an expression of loss of muscle mass (and hence weight loss) and decreased exercise tolerance. This weight change over time was considered as a shortcoming of studies accounting for a single BMI measurement. However, if this were true, then the same would apply for studies involving other variables measured once like bioelectrical impedance and other specific anthropometric surrogates of adiposity. More appropriate scientific consideration is to account for weight change as a unique risk factor corrected for BMI (i.e. lean or fat mass). This is functionally expressed by the higher mortality risk to remain un-fit or to have deteriorating CRF over-time. [22] A more complicating element of weight loss is the importance to differentiate intentional weight loss; probably coupled with exercise and improved CRF, and unintentional weight loss. In a cohort of 1,882 community dwelling elderly in Sao Paulo, having a mean age of 71 years, overweight had lower risk of death and obesity was not associated with higher risk of mortality. In a subpopulation of this database followed up for weight change, weight gain was associated with reducing mortality, except in the obese, and weight loss increased the risk of death in all BMI categories by 42-63%. [23] In a meta-analysis of 35,335 patients with mean age of 64 years in 12 studies on CAD patients, observational weight loss is associated with increased adverse cardiovascular events, while presumed intentional weight loss is associated with lower clinical events. [24] The same findings were found among 4869 men aged 56 to 75 years from 24 British towns followed up for 7 years, in a prospective study on intentional versus unintentional (observational) weight loss and all-cause mortality. [25] Self-intentional weight loss had a greater benefit in men who were greater in overweight and in those of the younger category, owing to reduction in non-cardiovascular mortality. On the other hand, physician-directed intentional weight loss had a benefit from reduction in all-cause mortality. In an older study which collected prospective data from a survey on 49,337 overweight white men aged 40-64 years over 12 years interval, the mortality effects of intentional weight loss was measured. [26] In the sub-cohort of 36,280 participants with no reported health conditions, intentional weight loss of more than 20 pounds increased diabetes-associated mortality by 48%. Whereas, in 13,057 overweight men with initially reported health conditions, intentional weight loss more than 20 pounds increased cancer mortality by 25%, and decreased diabetes-associated mortality by 32%. In fact, healthy individuals who were overweight or obese, were advised to change their life-style and CRF profile rather than losing weight in order to impact longevity. [27] In a population of 6,492 congestive heart failure patients followed up for 10 years for weight-change (≥ 5% decrease or ≥ 7% increase in BMI or other

anthropometric measurements), weight change was linked to increased risk of mortality. [28] In a study on 42,099 middle-aged Austrian men and women, followed-up for 5 to 12 years for BMI changes, all-cause mortality was assessed. [29] There was no increased risk of over-all mortality in individuals who remained in the categorical BMI of normal or overweight during the whole follow-up. However, the risk was increased in the obese. Gender differentiation increased risk of mortality for weight gain in overweight and obese women. Loss of weight consistently increased all-cause mortality.

The origin of the BMI-mortality paradox

Although our observations seemed unusual, the counterintuitive relationship between BMI and mortality is not completely new to the medical literature. Epidemiologic studies in Western societies from the era before discovering the obesity paradox showed a longer life expectancy in the overweight and obese over those, who did not join the obesity epidemic. [30-32] In their study, Kalmijn and colleagues investigated the association between BMI, waist-to-hip ratio (WHR) and the sum of the subscapular and triceps skinfold thickness in a cohort of 3741 elderly Japanese-American men, between 1991 and 1993, aged between 71 and 93 years. [33] Follow-up period was 4.5 years in average and they clearly showed that BMI and skinfold thickness had consistent inverse relationships with mortality. However, the idea was totally surprising and confusing particularly when they found a direct association between WHR and mortality. In 2000, Landi and colleagues found in 18,316 hospitalized elderly individuals that the lowest mortality rate was associated with BMI ranging between 25.0 through 27.4 $kg.m^{-2}$. [34] Plotting the life-table of the younger group produced a hyperbolic curve with increased mortality at the lowest and highest BMI's. For the older group, increased mortality was associated with being underweight, whereas high BMI showed slight increase in mortality hazard. Others endorsed the BMI paradox in patients with chronic heart failure and in dialysis patients . [35, 36] Following these reports, a surge of publications proved the epidemiologic existence of the paradox in the elderly patients and in those suffering from chronic debilitating conditions. These observations along with others concerning different risk factors led to originating the concept of reverse epidemiology in chronic diseases. [37]

Evidence from medical research supporting the BMI paradox in chronic disease populations

Obesity is a known risk factor for cardiovascular atherosclerotic disease and particular obesity-related cancers among the general population. However, substantial evidence from large observational studies supports the existence of the BMI paradox in particular chronic disease populations. Patients with chronic heart failure and coronary artery disease and end-stage renal disease were among the first and most extensively studied. In a recent meta-analysis of 14 studies on

23,967 heart failure patients[38] the obesity paradox was present both in patients with and without preserved left ventricular function. However, it was better demonstrated in those with preserved ejection fraction. Similar results as found in chapter 2 were reported in very large meta-analyses concerning patients with chronic heart failure, acute coronary syndromes, and patients who underwent revascularization procedures. [38-42] All the mentioned meta-analyses showed increased risk of mortality in the underweight group of patients. They also report overweight and obese patients as being younger in age, and having more burden of co-morbid conditions particularly diabetes.

Singer and colleagues examined 9,073 adult patients who underwent lung transplantations in the US between 2005 and 2011. [43] Normal, overweight and Class I obesity patients had similar low-risk profile for 1-year mortality, whereas underweight patients (35% increase) and patients with class II & III obesity (approximately 2-fold) carried an increased risk of death at 1-year. They indicated that; in relation to plasma leptin levels, BMI is a specific (97%) but not a sensitive (26%) measure of total bodily fat. Reis et al examined the risk association between measures of adiposity and overall mortality over 12 years follow-up in 12,228 adults aged 30-102 years. [44] Higher BMI's were associated with improved survival in both genders. In addition, we already reviewed two large meta-analyses and other large observational studies confirming the paradox determined in chapter 4.

The Myth of the Unfit Larger Bodies

Sawada et al recently conducted a study on 8760 Japanese male participants who were employees of the Tokyo Gas Company, who were followed up for cancer mortality to the year of 2003. [45] They found an inversely proportional relation of cardiorespiratory fitness (CRF) to cancer mortality. They based CRF definition on a submaximal exercise test on a cycle ergometer. Through subgrouping patients according to their CRF profile, they could explain the causes of decreased cancer mortality among higher BMI category as of having better cardiorespiratory fitness profile. Surprisingly, these results have a close relation to our findings shown in Chapter 2 when we sub-grouped our BMI categories according to their pulmonary function testing profile.

Major literature reviews of the obesity paradox; including our chapter 5, did not mention the importance of CRF as an important unmeasured variable in studies on BMI and mortality. In fact, this consideration was not completely overlooked in corresponding research.[46-49]

The contribution of fat-free mass to longevity

Body mass index does not necessarily indicate a fat index. Increased muscle mass had been linked to longevity and improved cardio-metabolic risk. [50, 51] Different morphologic and compositional types of obesity might exist in different proportions among patients with the same BMI. Thus the composition and distribution of body fat might differ from one individual to another. Central (i.e. visceral, android) adiposity was suggested to be associated with atherosclerotic and cardio-metabolic disease risk mediated by leptin and other mediators causing insulin-resisting, pro-inflammatory cascade. This is opposed by the anti-inflammatory and insulin sensitizing actions of peripheral (i.e. gynoid) adiposity secreting adiponectin and other mediators. A complex genetic, gender, racial, habitual, adipokine and perhaps neuro-hormonal factors play regulatory roles to define this. Not confined to adiposity, BMI also reflect the important component of muscle (fat-free) mass, which undoubtedly deters the injurious cascade of inflammatory cytokines associated with central adiposity by neutralizing and anti-inflammatory actions. [52]

It was shown by many studies that BMI is a sensitive but non-specific index of body adiposity. [53, 54] More accurate estimates of adiposity particularly bioelectric impedance showed the gapping misses given by BMI in comparative studies. [54] Thus, it limits the identification of obesity and includes other cases inside its set range. This is one element explaining how the risk of increasing BMI might be ameliorated in retrospective analyses. Other anthropometric measurements; and to a better extent ratios, proved to have increased, but not high, specificity concerning adiposity. [55]

Beyond the chronic disease populations: The BMI paradox in the general surgical populations

Previous suggestive explanations of the BMI paradox relied on its association with chronic cachectic diseases. [56] Early observations linked the phenomenon to chronic heart failure and end-stage renal disease. [35, 36, 38, 39] These reports were followed by studies exploring a possible association with other chronic conditions such as chronic obstructive pulmonary disease and coronary artery disease. [57-59] However, two challenging questions about the extent and range of involvement in this dynamic phenomenon were still unanswered. For the first, we conducted a trial in chapter 3 to evaluate a broad-spectrum general surgical population for the possibility to find the BMI paradox correlation. Our population was moderate with respect to the severity of co-existing morbidities, with a variable burden of risk factors making this population representative of the wider general medical population. In January 2013, Flegal and his colleagues published a meta-analysis in JAMA, which enrolled 2.88 million individuals from 97 studies, examined for mortality association with BMI. [60] Overweight and

class I obesity were associated with lower hazard of death from all-causes, whereas overall-obesity as well as obesity class II and III were associated with increased mortality hazard. Analysis by age shows a better form of the paradox for patients aged 65 years and higher, and in such case severe forms of obesity carry insignificant relationship with mortality. These findings point to other factors contributing to the paradox rather than chronic debilitating conditions. Furthermore, there is a growing belief that the role of the larger muscle mass in overweight and early obesity are causes of survival advantages of these groups; a reflection of the unmeasured "fat : muscle" ratio. [46, 50, 61, 62]

The second question is: whether the strength of the effect would be so obvious that it can predict outcome at a short follow-up such as the post-procedural and hospital stay outcome? We conducted in chapter 3 an analysis correlating BMI categories to the shorter postoperative 30-day mortality and length of hospital stay. That correlation was found true for the overweight only. Mullen and colleagues conducted a large observational study which showed the counterintuitive association between BMI and mortality is even true for the limited postoperative period. [63] This study reviewed 118,707 non-bariatric general surgical patients. In their study, the correlation between BMI and short-term mortality represented a unique shape with highest risk among those who were underweight, and with risk reduction among overweight and obesity type I and II patients. Other studies showed a similar correlation between BMI, perioperative mortality and length of hospital stay. Landi et al. conducted an analysis from a large Italian observational database showing hospitalization information for 18,316 geriatric patients admitted to 79 medical centers. [34] The same hyperbolic curve showed in their correlation between BMI and mortality with a unique preferential response for the older individuals. Obesity was a predictor of improved 30-day mortality in critically ill patients. [64, 65] In cardiothoracic surgical patients, better outcome was reported in the overweighed and obese, and attributed to better intraoperative and postoperative hemostasis, better hemodynamic tolerance and absence of increased early postoperative mortality; against the former belief. [66-72] Being underweight was a consistent risk factor for poor outcome and increased early mortality.

Would the categorical classification of BMI be responsible for the paradox?

Several studies revealed limitations caused by grouping patients according to the WHO standard categorization. [73, 74] Specific population and ethnic features must be considered. [45, 75-80] For example European studies defined a higher cutoff for atherosclerotic risk [75, 81], than studies on Asian populations [78-80].

Ethnic and racial factors

In a recent angiographic study of white and black races, the morbidly obese patients were found to have an ameliorated burden of coronary artery disease than their lean counterparts. [81] In a study of a subsample population of 4,489 non-institutionalized survey participants aged >60 years in the United States NANHES III survey database, BMI and other specific measures of adiposity were inversely proportional with cardiovascular and all-cause mortality. [82]

Limitations of our Interpretations of the BMI paradox:

(A) The standard BMI equation:

BMI is the result from dividing weight by the second exponential power of height. Many mathematicians advocated that the weight exponent of two should better be raised to a value between two and three in order to reflect bodily mass more accurately. This had led to the introduction of the *"new BMI"* in 2013 by Trefethenof, from the Mathematical Institute at the University of Oxford. Height in the equation is raised to the exponent of 2.5. The use of this equation is debated.

New BMI = 1.3 * weight (kg) / height (m) ^2.5 = 5734 * weight (lb) / height (in) ^ 2.5

In an ageing world, loss of a few centimeters of height in geriatrics adds another variable to the criticized equation. However, this new assumption required correlation studies to prove its value as compared to the standard BMI. In contrast to what is expected from this assumption, a recent study found the new BMI not superior to the traditional BMI in predicting postoperative complications following colo-rectal cancer surgery. [83]

(B) Is BMI per se an absolute risk factor for mortality?

With the progressive elucidation of the BMI paradox in different medical and surgical populations, it became important to distinguish the difference between risk association of a single factor such as BMI with a certain disease condition, and fatality from such disease. This is probably due to the fact that treatment of diseases prone to become clinically evident at an earlier age would ameliorate their functional impairment at a later stage of life, and would promote a state of parallelism or adaptation between these corrected morbidities and a functional state of life. This should definitely affect mortality rates from such treated conditions. Early presentation of overweighed individuals to

medical care; expected to be at risk of acquiring morbid conditions such as diabetes and hyperlipidemia, probably contributes to this effect.

(C) Sensitivity versus specificity of BMI for adiposity:

Another aspect of the paradox may be due to the sensitivity and specificity of BMI for associated risks and prediction power. The composition of BMI consisting in two different types of tissues (i.e. muscles (lean fat-free mass) and fat) and two metabolically active types of fat (i.e. central and peripheral) is making this more complicated . BMI is criticized of being a sensitive but non-specific indicator of central adiposity. A group of researchers studied a large European patient population for the cardiovascular mortality risk associated with multiple anthropometric measurements including BMI, waist circumference (WC), waist-to-hip ratio (WHR), waist-to-stature ratio (WSR), A Body Shape Index (ABSI) and waist-to-hip-to-height ratio (WHHR). Over a median follow-up period of 7.9 years, they found BMI carrying the lowest association value among all. [84] When these researchers repeated their analysis for all-cause mortality, the same relationship was shown. Whereas all other anthropometric measurements attained directly proportional linear fashions with all-cause and cardiovascular mortalities, the BMI plots were J-shaped. [81] This has been confirmed in patients older than 60 years. [50] A meta-regression analysis of 18 prospective cohort studies yielding 689, 465 total number of participants and 48, 421 deaths during 5-24 years of follow-up showed a hyperbolic U-shaped relationship between BMI and mortality, whereas WHR, WC and WHtR had a linear relationship. [85] A meta-analysis of 31 articles used a receiver operating characteristics (ROC) curves for assessing the discriminatory power of BMI, WC and waist-to-height ratio (WHtR) for cardio-metabolic risk and general cardiovascular outcomes (CVD). Using data on all outcomes in more than 300,000 patients, WHtR had the highest prediction. WHtR improved discrimination by 4-5% than BMI, while WC improved it by 3% than BMI. [86]

(D) Limitations of retrospective data studies:

We have mentioned earlier the limitation of retrospective research. Unknown confounders may bias the results.

Conciliating our results to other research findings

In our reports, we never intended to simplify our early results by saying: the fatter, the healthier to be. On the contrary, undoubted evidence from literature had shown the negative effects of adiposity on long-term outcomes. However, the BMI is a complicated unit of measurement gathering opposing parties including lean-mass, pro-inflammatory and anti-inflammatory adipose tissues. The complexity

of its formation in a human individual is complex and perhaps beyond our understanding, however, we can measure the longitudinal consequences of BMI in different populations in retrospective analyses. The longitudinal advantage of healthy life-style, CRF exercises and proper nutrition are undoubted; the same as the disadvantages of gathered adiposity. Other classical explanations mentioned in our review article in chapter 5 are widely accepted in the medical community. Being deficient in critical information such as the different proportions of central and peripheral fat, the CRF of the population and the amount of lean mass, is known for retrospective studies, but is a merit used to enlighten future prospective research.

Part II: The Intraoperative Period as a Continuum to Perioperative Evaluation

It becomes clear that the perioperative management of the surgical patient may have an impact not only on the immediate postoperative but also on the long-term outcome. [87-89] The primary goal is to ensure that surgical patients not only survive but also benefit from major surgery. Further goals are reducing risk factors and optimization of chronic co-morbidities. The initiation of secondary prevention of atherosclerotic disease prior to and after elective (vascular) surgery is in this perspective of particular importance. Anesthesiologists have now to extend their activities from intraoperative care to preoperative and postoperative care. The use of and communication about valuable information gained from the peri-operative period and the response of initiated therapy will be necessary to improve outcome and attain the ultimate goal of surgery.

Our main findings in this part indicate major advantages from the use of echocardiography in the peri-operative management of the vascular surgical patient. We have shown the superiority of intraoperative transesophageal echocardiography over preoperative dobutamine stress echocardiography in predicting the location of intraoperative and postoperative ischemic events. These findings and the lack of significance of the anesthetic technique used, intraoperative fluid management and hemodynamic variables suggest that imbalance between oxygen supply and demand is not the mechanism of perioperative myocardial ischemia in peripheral arterial disease patients. The value of ischemia-targeted echocardiography was evident over mere resting echocardiographic results. The high incidence of clinically detected and subclinical myocardial ischemia in this population warrants a stronger emphasis on the myocardial ischemic risk in this population. Our results match with results from other prospective controlled studies [90] examining the efficacy of coronary interventions prior to non-cardiac surgery. All studies indicate the superiority of global anti-ischemic management over invasive “focal” interventional management in prophylaxis against later myocardial ischemia and/or infarction in high-risk populations.

In the second chapter of this part (i.e. Chapter 7), utilization of preoperative resting echocardiography showed the high prevalence of left ventricular dysfunction in the peripheral arterial disease population mounting to 50%. Whereas only one-fifth (20%) of these affected patients was symptomatic, the rest was divided between asymptomatic LV systolic or diastolic dysfunctions. Unfortunately, and as a natural consequence, the implementation of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA) guidelines on the perioperative medical management of such patients was far from optimal. So there is room for improvement probably leading to a better outcome.

Because of the importance of cardiac events in the vascular surgical patient, it seems very interesting for clinicians to predict and prevent perioperative myocardial ischemia and infarction and implement evidence-based guidelines. [91] The incidence of intraoperative myocardial ischemia is said to be low due to lower adrenergic response under anesthesia and is influenced by optimal anesthetic management. Due to the variety of intraoperative anesthesia and surgery-related stressors influencing the homeostatic mechanisms in the vascular patient, the intraoperative setting can be considered as an ultimate stress test for myocardial ischemic events. Monitoring such effects on the vascular patient myocardium can yield important information about the occurrence of perioperative myocardial ischemia and infarction. Dobutamine stress echocardiography is an established risk estimate and accepted stress testing method in high- risk vascular surgical patients If the surgical setting could be utilized to analyze perioperative ischemic events, additional imaging by CT or MRI could elucidate the mechanism of perioperative myocardial ischemia and infarction. Consequently, targeted prophylaxis and therapy would be possible.

Despite preoperative optimization, the incidence of perioperative myocardial ischemia in this population appears to be high. There is a strong evidence that subclinical ischemic events (featured by elevated troponins only) are related to adverse long-term cardiac outcomes. [92-94] Because those events can occur both intraoperatively as well as postoperatively, intraoperative transesophageal echocardiography may complete the range of electrical and biochemical detection methods for those events occurring in the immediate perioperative phase. The appropriate management in subclinical myocardial ischemia is still to be determined. As 10% of these patients die within 30 days after operation, there is still room for improvement of the outcome of the surgical patient.

References

1. Das JR, Eberhardt RT. Contemporary risk assessment and cardiovascular outcomes in peripheral arterial disease. Cardiovasc Hematol Disord Drug Targets. 2013 Dec;13(3):185-96.

2. Armstrong EJ1, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, Yeo KK, Anderson D, Amsterdam EA, Laird JR. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. J Am Heart Assoc. 2014 Apr 10; 3(2):e000697.

3. Subherwal S1, Bhatt DL, Li S, Wang TY, Thomas L, Alexander KP, Patel MR, Ohman EM, Gibler WB, Peterson ED, Roe MT. Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. Circ Cardiovasc Qual Outcomes. 2012 Jul 1; 5(4):541-9.

4. Lifshitz F, Lifshitz JZ. Globesity: the root causes of the obesity epidemic in the USA and now worldwide. Pediatr Endocrinol Rev. 2014 Sep;12(1):17-34

5. Mitchell NS1, Catenacci VA, Wyatt HR, Hill JO. Obesity: overview of an epidemic. Psychiatr Clin North Am. 2011 Dec;34(4):717-32

6. Hill JO. Understanding and addressing the epidemic of obesity: an energy balance perspective. Endocr Rev. 2006 Dec; 27(7):750-61

7. World Health Organization (WHO) Health statistics and information systems. WHO's Study of Global Aging and Adult Health, SAGE Longitudinal Multicountry Study; http://www.who.int/healthinfo/sage/cohorts/en/

8. Ladabaum U, Mannalithara A, Myer PA, Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. Am J Med. 2014 Aug; 127(8): 717-727.e12

9. Sharma A, Vallakati A, Einstein AJ, Lavie CJ, Arbab-Zadeh A, Lopez-Jimenez F, Mukherjee D, Lichstein E. Relationship of body mass index with total mortality, cardiovascular mortality, and myocardial infarction after coronary revascularization: evidence from a meta-analysis. Mayo Clin Proc. 2014 Aug;89(8):1080-100

10. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007 Nov 7;298(17):2028-37

11. Roh L, Braun J, Chiolero A, Bopp M, Rohrmann S, Faeh D; Swiss National Cohort Study Group. Mortality risk associated with underweight: a census-linked cohort of 31,578 individuals with up to 32 years of follow-up. BMC Public Health. 2014 Apr 16;14:371. doi: 10.1186/1471-2458-14-371.

12. Soenen S, Chapman IM. Body weight, anorexia, and undernutrition in older people. J Am Med Dir Assoc. 2013 Sep;14(9):642-8

13. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - a mini-review. Gerontology. 2014;60(4):294-305

14. Bing C. Lipid mobilization in cachexia: mechanisms and mediators. Curr Opin Support Palliat Care. 2011 Dec;5(4):356-60

15. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. Clin Nutr. 2007 Aug;26(4):389-99

16. Balaskó M, Soós S, Székely M, Pétervári E. Leptin and aging: Review and questions with particular emphasis on its role in the central regulation of energy balance. J Chem Neuroanat. 2014 Sep 16. pii: S0891-0618(14)00083-0. doi: 10.1016/j.jchemneu.2014.08.006

17. Engineer DR, Garcia JM. Leptin in anorexia and cachexia syndrome. Int J Pept. 2012;2012:287457

18. Buskermolen S, Langius JA, Kruizenga HM, Ligthart-Melis GC, Heymans MW, Verheul HM. Weight loss of 5% or more predicts loss of fat-free mass during palliative chemotherapy in patients with advanced cancer: a pilot study. Nutr Cancer. 2012 Aug;64(6):826-32

19. Tsai S. Importance of lean body mass in the oncologic patient. Nutr Clin Pract. 2012 Oct;27(5):593-8

20. Carter S, Caron A, Richard D, Picard F. Role of leptin resistance in the development of obesity in older patients. Clin Interv Aging. 2013;8:829-44

21. Watt KD. Is 40 the new 30? Transpl Int. 2014 Nov 11. doi: 10.1111/tri.12487

22. Zhang P1, Sui X, Hand GA, Hébert JR, Blair SN. Association of changes in fitness and body composition with cancer mortality in men. Med Sci Sports Exerc. 2014 Jul;46(7):1366-74

23. Suemoto CK, Lebrao ML, Duarte YA, Danaei G. Effects of Body Mass Index, Abdominal Obesity, and Type 2 Diabetes on Mortality in Community-Dwelling Elderly in Sao Paulo, Brazil: Analysis of Prospective Data From the SABE Study. J Gerontol A Biol Sci Med Sci. 2014 Sep 9. pii: glu165

24. Pack QR, Rodriguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, Lopez-Jimenez F. he prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. Mayo Clin Proc. 2014 Oct;89(10):1368-77

25. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. Arch Intern Med. 2005 May 9;165(9):1035-40

26. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in overweight white men aged 40-64 years. Am J Epidemiol. 1999 Mar 15;149(6):491-503

27. Harrington M1, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. Nutr Res Rev. 2009 Jun;22(1):93-108

28. Aranda RM1, Puerto JL, Andrey JL, Escobar MA, García-Egido A, Romero SP, Pedrosa MJ, Gómez F. Fluctuations of the anthropometric indices and mortality of patients with incident heart failure: a prospective study in the community. Int J Clin Pract. 2014 Jul 16. doi: 10.1111/ijcp.12479

29. Klenk J1, Rapp K1, Ulmer H2, Concin H3, Nagel G4. Changes of body mass index in relation to mortality: results of a cohort of 42,099 adults. PLoS One. 2014 Jan 8;9(1):e84817

30. Lev-Ran A. Human obesity: an evolutionary approach to understanding our bulging waistline. Diabetes Metab Res Rev 2001;17:347-62.

31. Darnton-Hill I, Coyne ET. Feast and famine: socioeconomic disparities in global nutrition and health. Public Health Nutr 1998; 1:23–31

32. Menotti A, Blackburn H, Kromhout D, et al. Cardiovascular risk factors as determinants of 25-year all-cause mortality in the seven countries study. Eur J Epidemiol 2001; 17:337-46

33. Kalmijn S, Curb JD, Rodriguez BL, Yano K, Abbott RD. The association of body weight and anthropometry with mortality in elderly men: the Honolulu Heart Program. Int J Obes Relat Metab Disord 1999;23:395-402

34. Landi F, Onder G, Gambassi G, Pedone C, Carbonin P, Bernabei R. Body mass index and mortality among hospitalized patients. Arch Intern Med 2000;160:2641-4

35. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2001;38:789-95

36. Leavey SF, McCullough K, Hecking E, Goodkin D, Port FK, Young EW. Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2001;16:2386-94

37. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol. 2004 Apr 21; 43(8): 1439-44

38. Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, Swedberg K, Maggioni A, Gamble G, Ariti C, Earle N, Whalley G, Poppe KK, Doughty RN, Bayes-Genis A; Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. Int J Obes (Lond). 2014 Aug;38(8):1110-4

39. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J. 2008 Jul;156(1):13-22

40. Niedziela J, Hudzik B, Niedziela N, Gąsior M, Gierlotka M, Wasilewski J, Myrda K, Lekston A, Poloński L, Rozentryt P. The obesity paradox in acute coronary syndrome: a meta-analysis. Eur J Epidemiol. 2014 Nov;29(11):801-12

41. Li YH, Lin GM, Lin CL, Wang JH, Han CL. Relation of body mass index to mortality among patients with percutaneous coronary intervention longer than 5 years follow-up: a meta-analysis. Int J Cardiol. 2013 Oct 9;168(4):4315-8

42. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet. 2006 Aug 19;368(9536):666-78

43. Singer JP, Peterson ER, Snyder ME, Katz PP, Golden JA, D'Ovidio F, Bacchetta M, Sonett JR, Kukreja J, Shah L, Robbins H, Van Horn K, Shah RJ, Diamond JM, Wickersham N, Sun L, Hays S, Arcasoy SM, Palmer SM, Ware LB, Christie JD, Lederer DJ. Body composition and mortality after adult lung transplantation in the United States. Am J Respir Crit Care Med. 2014 Nov 1;190(9):1012-21

44. Reis JP, Macera CA, Araneta MR, Lindsay SP, Marshall SJ, Wingard DL. Comparison of overall obesity and body fat distribution in predicting risk of mortality. Obesity (Silver Spring). 2009 Jun;17(6):1232-9

45. Sawada SS, Lee IM, Naito H, Kakigi R, Goto S, Kanazawa M, Okamoto T, Tsukamoto K, Muto T, Tanaka H, Blair SN. Cardiorespiratory fitness, body mass index, and cancer mortality: a cohort study of Japanese men. BMC Public Health. 2014 Sep 27;14:1012

46. Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. Nat Rev Endocrinol. 2014 Sep 30. doi: 10.1038/nrendo.2014.165.

47. Lavie CJ, Schutter AD, Archer E, McAuley PA, Blair SN. Obesity and prognosis in chronic diseases--impact of cardiorespiratory fitness in the obesity paradox. Curr Sports Med Rep. 2014 Jul-Aug;13(4):240-5

48. McAuley PA, Beavers KM. Contribution of cardiorespiratory fitness to the obesity paradox. Prog Cardiovasc Dis. 2014 Jan-Feb;56(4):434-40

49. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. J Am Coll Cardiol. 2014 Apr 15;63(14):1345-54

50. Stenholm S, Mehta NK, Elo IT, Heliövaara M, Koskinen S, Aromaa A. Obesity and muscle strength as long-term determinants of all-cause mortality--a 33-year follow-up of the Mini-Finland Health Examination Survey. Int J Obes (Lond). 2014 Aug;38(8):1126-32

51. De Schutter A, Lavie CJ, Kachur S, Patel DA, Milani RV. Body composition and mortality in a large cohort with preserved ejection fraction: untangling the obesity paradox. Mayo Clin Proc. 2014 Aug;89(8):1072-9

52. Carter S, Caron A, Richard D, Picard F. Role of leptin resistance in the development of obesity in older patients. Clin Interv Aging. 2013;8:829-44

53. Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J, Allison TG, Batsis JA, Sert-Kuniyoshi FH, Lopez-Jimenez F. Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes (Lond). 2008 Jun;32(6):959-66

54. Liu LN, Miaskowski C, Wang JS, Chen SC, Chen ML. Accuracy of body mass index to determine obesity in women with breast cancer: an observational study of Taiwanese sample. Int J Nurs Stud. 2010 Aug;47(8):994-1000

55. Dalton M, Cameron AJ, Zimmet PZ, Shaw JE, Jolley D, Dunstan DW, Welborn TA; AusDiab Steering Committee.. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. J Intern Med. 2003 Dec;254(6):555-63

56. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, Kovesdy CP, Younessi H, Anker SD, Morley JE. Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care. 2007 Jul;10(4):433-42

57. Gruberg L, Mercado N, Milo S, Boersma E, Disco C, van Es GA, Lemos PA, Ben Tzvi M, Wijns W, Unger F, Beyar R, Serruys PW; Arterial Revascularization Therapies Study Investigators. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: The obesity paradox II? Am J Cardiol. 2005 Feb 15;95(4):439-44

58. Rubinshtein R, Halon DA, Jaffe R, Shahla J, Lewis BS. Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. Am J Cardiol. 2006 May 1;97(9):1277-80

59. Lavie CJ, Ventura HO, Milani RV. The "obesity paradox": is smoking/lung disease the explanation? Chest. 2008 Nov;134(5):896-8

60. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013 Jan 2;309(1):71-82

61. Murphy RA, Reinders I, Garcia ME, Eiriksdottir G, Launer LJ, Benediktsson R, Gudnason V, Jonsson PV, Harris TB; Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik). Adipose tissue, muscle, and function: potential mediators of associations between body weight and mortality in older adults with type 2 diabetes. Diabetes Care. 2014 Dec;37(12):3213-9

62. Sabino PG, Silva BM, Brunetto AF. Nutritional status is related to fat-free mass, exercise capacity and inspiratory strength in severe chronic obstructive pulmonary disease patients. Clinics (Sao Paulo). 2010 Jun;65(6):599-605

63. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. Ann Surg. 2009 Jul;250(1):166-72

64. Robinson MK, Mogensen KM, Casey JD, McKane CK, Moromizato T, Rawn JD, Christopher KB. The Relationship Between Obesity, Nutritional Status, and Mortality in the Critically Ill. Crit Care Med. 2014 Oct 3. [Epub ahead of print]

65. Pickkers P, de Keizer N, Dusseljee J, Weerheijm D, van der Hoeven JG, Peek N. Body mass index is associated with hospital mortality in critically ill patients: an observational cohort study. Crit Care Med. 2013 Aug;41(8):1878-83

66. Paul S, Andrews W, Osakwe NC, Port JL, Lee PC, Stiles BM, Altorki NK. Perioperative Outcomes after Lung Resection in Obese Patients. Thorac Cardiovasc Surg. 2014 Jul 28. [Epub ahead of print]

67. Kindo M, Minh TH, Gerelli S, Meyer N, Schaeffer M, Perrier S, Bentz J, Announe T, Mommerot A, Collange O, Marguerite S, Thibaud A, Gros H, Billaud P, Mazzucotelli JP. The prothrombotic paradox of severe obesity after cardiac surgery under cardiopulmonary bypass. Thromb Res. 2014 Aug;134(2):346-53

68. Engel AM, McDonough S, Smith JM. Does an obese body mass index affect hospital outcomes after coronary artery bypass graft surgery? Ann Thorac Surg. 2009 Dec;88(6):1793-800

69. Reeves BC, Ascione R, Chamberlain MH, Angelini GD. Effect of body mass index on early outcomes in patients undergoing coronary artery bypass surgery. J Am Coll Cardiol. 2003 Aug 20;42(4):668-76

70. Shirzad M, Karimi A, Armadi SH, Marzban M, Abbasi K, Alinejad B, Moshtaghi N. Effects of body mass index on early outcome of coronary artery bypass surgery. Minerva Chir. 2009 Feb;64(1):17-23

71. Wiedemann D, Schachner T, Bonaros N, Weidinger F, Kolbitsch C, Friedrich G, Laufer G, Bonatti J. Does obesity affect operative times and perioperative outcome of patients undergoing totally endoscopic coronary artery bypass surgery? Interact Cardiovasc Thorac Surg. 2009 Aug;9(2):214-7

72. Tokmakoglu H. Operative and early results of coronary artery bypass grafting in female patients in different body mass indexes. J Cardiothorac Surg. 2010 Nov 26;5:119 doi: 10.1186/1749-8090-5-119.

73. Obesity: preventing and managing the global epidemic: report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253

74. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Am J Clin Nutr. 1998;68(4):899-917

75. Hadaegh F, Zabetian A, Sarbakhsh P, Khalili D, James WP, Azizi F. Appropriate cutoff values of anthropometric variables to predict cardiovascular outcomes: 7.6 years follow-up in an Iranian population. Int J Obes (Lond). 2009 Dec;33(12):1437-45

76. Mirmiran P, Esmaillzadeh A, Azizi F. Detection of cardiovascular risk factors by anthropometric measures in Tehranian adults: receiver operating characteristic (ROC) curve analysis. Eur J Clin Nutr. 2004 Aug;58(8):1110-8

77. Taylor AE, Ebrahim S, Ben-Shlomo Y, Martin RM, Whincup PH, Yarnell JW, Wannamethee SG, Lawlor DA. Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. Am J Clin Nutr. 2010 Mar;91(3):547-56

78. Pan S, Yu ZX, Ma YT, Liu F, Yang YN, Ma X, Fu ZY, Li XM, Xie X, Chen Y, Chen B, He CH. Appropriate body mass index and waist circumference cutoffs for categorization of overweight and central adiposity among Uighur adults in Xinjiang. PLoS One. 2013 Nov 7;8(11):e80185

79. Samsen M, Hanchaiphiboolkul S, Puthkhao P, Tantirittisak T, Towanabut S. Appropriate body mass index and waist circumference cutoffs for middle and older age group in Thailand: data of 19,621 participants from Thai epidemiologic stroke (TES) study. J Med Assoc Thai. 2012 Sep;95(9):1156-66

80. Inayama T, Higuchi Y, Tsunoda N3, Uchiyama H, Sakuma H. Associations between abdominal visceral fat and surrogate measures of obesity in Japanese Spinal Cord. 2014 Nov;52(11):836-41men with spinal cord injury.

81. Song X, Jousilahti P, Stehouwer CD, Söderberg S, Onat A, Laatikainen T, Yudkin JS, Dankner R, Morris R, Tuomilehto J, Qiao Q; for the DECODE Study Group. Cardiovascular and all-cause mortality in relation to various anthropometric measures of obesity in Europeans. Nutr Metab Cardiovasc Dis. 2014 Sep 20. pii: S0939-4753(14)00290-7. doi: 10.1016/j.numecd.2014.09.004

82. Stalls CM, Triplette MA, Viera AJ, Pathman DE, Cohen MG, Rossi JS. The association between body mass index and coronary artery disease severity: a comparison of black and white patients.Am Heart J. 2014 Apr;167(4):514-20

    Batsis JA1, Singh S, Lopez-Jimenez F. Anthropometric measurements and survival in older americans: results from the third national health and nutrition examination survey. J Nutr Health Aging. 2014;18(2):123-30

83. van Vugt JL, Cakir H, Kornmann VN, Doodeman HJ, Stoot JH, Boerma D, Houdijk AP, Hulsewé KW. The new Body Mass Index as a predictor of postoperative complications in elective colorectal cancer surgery. Clin Nutr. 2014 Aug 15. pii: S0261-5614(14)00210-6

84. Song X, Jousilahti P, Stehouwer CD, Söderberg S, Onat A, Laatikainen T, Yudkin JS, Dankner R, Morris R, Tuomilehto J, Qiao Q; for the DECODE Study Group. Comparison of various surrogate obesity indicators as predictors of cardiovascular mortality in four European populations.Nutr Metab Cardiovasc Dis. 2014 Sep 20. pii: S0939-4753(14)00290-7. doi: 10.1016/j.numecd.2014.09.004

85. Carmienke S, Freitag MH, Pischon T, Schlattmann P, Fankhaenel T, Goebel H, Gensichen J. General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. Eur J Clin Nutr. 2013 Jun;67(6):573-85

86. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev. 2012 Mar;13(3):275-86

87. Goei D, van Kuijk JP, Flu WJ, Hoeks SE, Chonchol M, Verhagen HJ, Bax JJ, Poldermans D. Usefulness of repeated N-terminal pro-B-type natriuretic peptide measurements as incremental predictor for long-term cardiovascular outcome after vascular surgery. Am J Cardiol. 2011;107:609-14

88. Wisman PP, Nolthenius RP, Tromp SC, Kelder JC, de Vries JP. Longer time interval between carotid cross-clamping and shunting is associated with increased 30-day stroke and death rate. Vasc Endovascular Surg 2011;45:335-9

89. Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg 2009;208:931-7

90. McFalls EO1, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004 Dec 30;351(27):2795-804

91. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C; Authors/Task Force Members. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014 Sep 14;35(35):2383-431

92. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012 Jun 6;307(21):2295-304

93. Nagele P, Brown F, Gage BF, Gibson DW, Miller JP, Jaffe AS, Apple FS, Scott MG. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. Am Heart J. 2013 Aug;166(2):325-332.e1

94. Weber M1, Luchner A, Seeberger M, Mueller C, Liebetrau C, Schlitt A, Apostolovic S, Jankovic R, Bankovic D, Jovic M, Mitrovic V, Nef H, Mollmann H, Hamm CW. Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery. Eur Heart J. 2013 Mar;34(11):853-62

Summary

Summary

Preoperative evaluation and perioperative management play a key role in postoperative outcome. However, this link is not always clear and often difficult to reveal. Many correctable risk factors must be considered by the anesthesiologist during careful preoperative evaluation, to guide the process of intraoperative management and postoperative follow-up towards an improved and more satisfactory outcome of the surgical patient.

This thesis is composed of two parts. In the first part we studied the inverted relationship between the preoperatively determined BMI and the long-term mortality in surgical patients: the phenomenon of "the body mass index paradox". It mainly included subjects suffering from peripheral artery disease, coronary artery disease, and polyvascular disease **(Chapters 1, 2 and 4)**. However, the existence of the phenomenon in the more generalized surgical population required to be established **(Chapter 3)**. This retrospective study, was performed in a large surgical population undergoing a wide variety of general surgery procedures to examine the association between BMI, and the length of hospital stay and mortality.

The body mass index - mortality paradox is a phenomenon, which require epidemiologic validation of its nature, prevalence, affected patient populations and influencing factors. The field of anesthesiology can prove a very helpful area for the epidemiologic study of this phenomenon as the routine inclusion and simplicity of weight and height measurements in hospitalized patients prior to their surgeries makes the study of this phenomenon by an anesthetist convenient. Erroneously, this phenomenon is commonly known as the obesity paradox although the paradoxical association also exists even more in the underweight patients.

In the second part, two studies were conducted to demonstrate the value of perioperative echocardiography as a powerful tool in the hands of perioperative anesthesiology physician, applying and interpreting the recommendations of the respective echocardiography and cardiology societies including the European Society of Cardiology (ESC), the American Society of Echocardiography (ASE) and the Society of Cardiovascular Anesthesiologists (SCA). Adherence to such recommendations based on clinical evidence is expected to decrease complication rates and improve postoperative outcome, i.e. quality of life and survival. These guidelines primarily target on perioperative anesthetic management beyond merely allowing a smooth surgical procedure.

Part I: The body mass index paradox

In the beginning of our studies, we examined a population of 5950 patients with known or suspected coronary artery disease for the existence of BMI paradox; **(Chapter 1)**. We positively identified an inverse relationship between BMI and long-term mortality from all causes and cardiac mortality; so that lower BMI groups carry a higher risk association with long-term overall mortality and cardiac death, than the higher BMI categories.

In **Chapter 2**, our results showed that mortality rates decreased significantly with increasing BMI in a group of peripheral arterial disease patients who underwent pulmonary function testing prior to their surgery. Further sub-classification of our patients according to COPD severity showed that underweight patients are

associated with more severe form of the COPD. Correction for COPD severity in multivariate analysis eliminated the significant association between underweight patients and mortality, but not the survival benefit associated with higher BMI groups.

Chapter 3 focused on the risk of polyvascular disease and its possible influence on the BMI paradox. Although all risk factors were equally targeted with medical therapy in all BMI categories, being underweight was an independent risk for decreased survival and showed the lowest usage of cardioprotective medication. However, the overweight category of patients showed the highest prevalence of polyvascular disease and utilization of cardioprotective medication and was associated with improved survival against long-term all-cause mortality. There was insignificant interaction term between BMI, presence of polyvascular disease and long-term outcome in this population.

In Chapter 4 the phenomenon of BMI paradox differed in short-term from long-term follow-up. Although only overweight patients showed improved survival at short-term, nevertheless, BMI was paradoxically associated with the length of hospital stay. The existence of BMI inverse relationship to long-term overall mortality was clearly shown in this population. Further examination of the causes of mortality in deceased patients revealed that lower BMI was associated with cancer death, whereas only overweight patients had improved survival from cardiovascular causes.

In **Chapter 5**, we performed a review from the literature on the obesity paradox in a general surgery population. Patients at the extremes of BMI, both the underweight and the morbid obese seem to have the highest postoperative morbidity and mortality hazard, which even persists at long-term. The cause of the obesity paradox is probably multi-factorial. This offers potential for future research in order to improve outcomes for persons on both sides of the 'optimum BMI'.

Part II: Expanding the Utility of Perioperative and Intraoperative Echocardiography

In the second part of this thesis, we included two prospective studies. The study presented in **Chapter 6** showed a higher rate of inducible ischemia during Dobutamine Stress Echocardiography (DSE) than intraoperatively detected by TEE, with poor agreement in the location of myocardial ischemia of respective patients undergoing major vascular surgery. The rate of subclinical ischemia in this small population detected by elevation of cardiac troponin levels without further manifestations approached 15%, whereas that of myocardial infarction was 11%. Cardiac death occurred in 6% of patients. DSE could predict the occurrence of intraoperative and postoperative ischemic changes and rest wall motion abnormalities but not the location of new wall motion abnormalities. In all postoperative cases of MI, there was 100% prediction of the location of MI by intraoperative TEE, whereas preoperative stress testing predicted the location correctly in only one third of the cases. This study added a proof to the hypothesized benefit of global medical management of cardiac

ischemic patients over focused therapy with coronary interventions attacking particular culprit lesions or particular coronary artery branches prior to vascular surgery.

Finally, **Chapter 7** showed that left ventricular dysfunction is present in one-half of patients undergoing vascular procedures. Of those only 20% were symptomatic and the remaining 80% were asymptomatic and equally divided between systolic and diastolic dysfunctions. Adherence to the ESC recommended therapy was found in only one third of those patients as identified by the utilization of angiotensin-converting enzyme inhibitors/ angiotensin-receptor blockers and/or diuretics. These findings indicated insufficient management of this patients group compared to the guidelines of the ESC despite high prevalence of this problem in this particular population.

Nederlandse samenvatting

Preoperatief onderzoek en perioperatief management zijn belangrijke factoren die de postoperatieve uitkomst bepalen. De relatie tussen de factoren en de uitkomst is niet altijd duidelijk en soms lastig te leggen. De anesthesioloog moet vele corrigeerbare factoren beschouwen bij het uitvoeren van het preoperatief onderzoek. Dit moet voor de chirurgische patiënt leiden tot een verbeterde uitkomst van het intraoperatieve proces en de postoperatieve follow-up periode.

Dit proefschrift bestaat uit twee delen. In het eerste deel wordt het fenomeen van de omgekeerde relatie tussen het preoperatief bepaalde BMI en de lange termijn sterfte bij chirurgische patiënten bestudeerd: de *body mass index paradox*. Er is specifiek onderzoek gedaan naar patiënten die leden aan perifeer arterieel vaatlijden, coronarialijden en gegeneraliseerd vaatlijden. (**hoofdstukken 1,2, en 4**). Het optreden van dit fenomeen in een populatie van patiënten die algemeen chirurgische operaties ondergingen, was tot nu toe niet vastgesteld (**hoofdstuk 3**). Deze retrospectieve studie werd uitgevoerd in een grote algemeen chirurgische populatie om de relatie vast te stellen tussen BMI enerzijds en de lengte van verblijf in het ziekenhuis en de mortaliteit anderzijds vast te stellen.

De BMI-mortaliteit paradox is een fenomeen dat epidemiologisch gevalideerd dient te worden om vast te stellen wat de oorzaak, de prevalentie en de beïnvloedende factoren zijn en welke patiënten populatie het betreft . De anesthesiologie kan hierbij de epidemiologische studies ondersteunen, omdat lengte en gewicht naast ander relevante gegevens immers routinematig opgenomen worden in het preoperatieve dossier . Abusievelijk is de BMI-paradox meer bekend bij het publiek en ook bij medici als de *obesity paradox* ondanks het feit dat de paradox nog het sterkst voordoet bij patiënten met ondergewicht.

In het tweede deel worden twee studies beschreven die de waarde aantonen van perioperatieve echocardiografie, als een belangrijk hulpmiddel voor de perioperatief werkzame anesthesioloog. Met gegevens verkregen met echocardiografie kunnen de richtlijnen van de respectievelijke cardiologische, echografische en anesthesiologische verenigingen, zoals de European Society of Cardiology (ESC), American Society of Echocardiography (ASE) en de Society of Cardiovascular Anesthesiologists (SCA), beter geïmplementeerd worden. Het opvolgen van deze richtlijnen die op klinisch bewijs gestoeld zijn, zou naar verwachting moeten leiden tot een verlaging van het aantal complicaties en een verbetering van de klinische uitkomst, te weten kwaliteit van leven en overleving. Deze richtlijnen gaan primair

meer over het perioperatieve anesthesiologisch beleid dan over de wijze waarop een chirurgische ingreep gefaciliteerd moet worden.

Deel I: de *body mass index paradox.*

Ons onderzoek begon met het de vraag of de BMI paradox aanwezig was bij 5950 patiënten bekend met of verdacht van coronarialijden (**hoofdstuk 1**). Wij vonden inderdaad een omgekeerde relatie tussen BMI en lange termijn mortaliteit ten gevolge van alle doodsoorzaken, maar ook van cardiale doodsoorzaken. De patiënten met een lage BMI hadden een hoger risico op lange termijn sterfte door alle oorzaken en hartdood dan de patiënten met een hogere BMI.

In **hoofdstuk 2** toonden wij aan dat de mortaliteit bij patiënten met perifeer arterieel vaatlijden die vooraf aan hun operatie een longfunctie onderzoek ondergingen, duidelijk afnam met de toename van de BMI. Verdere sub-classificatie van onze patiënten naar ernst van de COPD liet zien dat patiënten met ondergewicht vaker aan een ernstiger vorm van COPD leden. Correctie voor de ernst van de COPD in de multivariate analyse elimineerde de significante associatie tussen patiënten met ondergewicht en mortaliteit, maar niet de associatie tussen toegenomen overleving en een hoger BMI.

Hoofdstuk 3 richt zich op de risico's van gegeneraliseerd vaatlijden en de invloed op de BMI paradox. Hoewel voor alle risico factoren in alle BMI categorieën dezelfde streefwaarden voor de medicamenteuze therapie gehanteerd werden, bleek ondergewicht een onafhankelijke voorspeller voor afgenomen overleving maar ook voor het laagste gebruik van cardiale medicatie. De groep met overgewicht toonde, daarentegen, niet alleen de hoogste prevalentie van gegeneraliseerd vaatlijden en gebruik van cardiale medicatie, maar ook een toegenomen overleving wanneer naar overlijden ten gevolge van alle doodsoorzaken gekeken wordt. De relatie tussen BMI, gegeneraliseerd vaatlijden en lange termijn uitkomsten was in de groep patiënten niet significant.

In **hoofdstuk 4** blijkt het fenomeen van de BMI paradox verschillend te zijn met betrekking tot korte en lange termijn overleving. Hoewel uitsluitend de patiënten met overgewicht op korte termijn een toegenomen overleving hadden, was daarentegen BMI paradoxaal gerelateerd aan de lengte van het verblijf in het ziekenhuis. Het bestaan van een omgekeerde relatie tussen BMI en lange termijn mortaliteit door alle doodsoorzaken was in deze groep patiënten duidelijk aanwezig. Verder onderzoek naar de doodsoorzaken bracht aan het licht dat een lagere BMI was geassocieerd met dood ten gevolge van kanker, terwijl patiënten met overgewicht een toegenomen overleving op cardiovasculair gebied toonden.

In **hoofdstuk 5** hebben wij een review van de literatuur over de BMI paradox in de algemeen chirurgische populatie geschreven. Patiënten aan de uiteinden van het spectrum, zowel die met ondergewicht als de morbide obese, blijken de hoogste postoperatieve morbiditeit en mortaliteitsrisico's te lopen. Ook op lange termijn blijkt dit het geval. De oorzaak van de BMI paradox is waarschijnlijk multifactorieel. Dit geeft weer mogelijkheden voor toekomstig onderzoek om de uitkomsten van patiënten aan de uiteinden van het BMI spectrum te verbeteren.

Deel II: De uitbreiding van het gebruik van perioperatieve en intraoperatieve echocardiografie.

Dit deel presenteert 2 prospectieve studies. De studie in **hoofdstuk 6** toont aan dat er vaker ischemie geprovoceerd wordt bij dobutamine stress echocardiografie (DSE) dan er ischemie tijdens operaties vastgesteld wordt met behulp van transoesophageale echocardiografie. Bovendien is er bij patiënten die grote vaatchirurgische ingrepen ondergaan een slechte correlatie tussen beide onderzoeken met betrekking tot de locatie waar de ischemie vastgesteld wordt. De frequentie van subklinische ischemie in deze patiëntengroep aangetoond door uitsluitend een stijging van het serumtroponine bedraagt 15% terwijl myocardinfarct in 11% voorkomt. De cardiale mortaliteit bedraagt 6%. DSE kan het optreden van intraoperatieve en postoperatieve ischemische veranderingen en blijvende wand bewegingsstoornissen in het hart voorspellen, maar niet de plaats waar dit op zal treden. Bij alle patiënten met een postoperatief hartinfarct werd de lokalisatie van het infarct met behulp van TEE in 100% correct voorspeld, terwijl DSE maar in een derde van de gevallen een juiste voorspelling van de lokalisatie opleverde. De studie geeft steun aan de gedachte dat algemene medicamenteuze behandeling van cardiale ischemie beter is dan lokale behandeling van laesies in de coronair arteriën voorafgaand aan een vaatchirurgische operatie.

Tot slot laat **hoofdstuk 7** zien dat dysfunctie van de linker hartkamer voorkomt in de helft van de patiënten die een vaatoperatie ondergaan. Hiervan is 20% van de patiënten symptomatisch. De 80% asymptomatische patiënten zijn gelijk verdeeld over systolische en diastolische dysfunctie. Slechts in een derde van de patiënten werden de ESC behandelrichtlijnen gevolgd. Het volgen van de richtlijnen werd afgeleid uit het gebruik van angiotensin converting enzyme remmers, en/of diuretica. Deze bevindingen tonen aan dat er sprake is van onderbehandeling van deze patiëntengroep ten opzichte van de ESC richtlijnen ondanks het veelvuldig voorkomen van dysfunctie van de linker hartkamer.

الملخص العربي

تقييم المرضى قبل الجراحة والإدارة الطبية المحيطة بالجراحة تلعب دورا رئيسيا في نتائج ما بعد الجراحة . ومع ذلك ، هذا الرابط لا يكون واضحا دائما وغالبا ما يصعب الكشف عنه . و يجب النظر في العديد من عوامل الخطورة و تصحيحها من قبل طبيب التخدير قبل الجراحة خلال تقييم دقيق قبل الإجراء ، لتوجيه عملية الإدارة الطبية أثناء الجراحة و متابعة المرضى بعد الجراحة نحو نتائج أفضل و مرضية أكثر للمريض الجراحي .

وتتكون هذه الأطروحة من جزئين ، في **الجزء الأول** تمت دراسة ظاهرة العلاقة المعكوسة بين مؤشر كتلة الجسم الذي تحدد قبل الجراحة ومعدل الوفيات على المدى الطويل في مرضى العمليات جراحية أو ما يسمى "مفارقة مؤشر كتلة الجسم" . هذه الدراسات تضمنت بشكل رئيسي مرضى يعانون من أمراض الشرايين المحيطية ، ومرض الشرايين التاجية ، و مرض الأوعية الدموية المحيطية المتعددة (الفصول الأول و الثاني و الرابع) . ومع ذلك ، فإن إثبات وجود هذه الظاهرة في تعداد المرضى الجراحيين الأكثر عموما هو أمر مطلوب إثباته (الفصل الثالث) . هذه الدراسة هي دراسة استعادية من حيث النوعية ، أجريت في تعداد ضخم من المرضى الجراحيين الذين خضعوا لمجموعة واسعة من الإجراءات الجراحية العامة ، و ذلك لدراسة العلاقة بين مؤشر كتلة الجسم من جهة ، وطول فترة الإقامة في المستشفى بعد إجراء الجراحة و معدل الوفيات بينهم في تلك الفترة و على المدى البعيد .

و المفارقة بين مؤشر كتلة الجسم و معدل الوفيات هي ظاهرة لوحظت في الآونة الأخيرة ، تتطلب التحقق من ما هيتها وبائيا ، وانتشارها ، والمرضى المتضمنين بها ، والعوامل المؤثرة فيها . إن مجال التخدير يمكن أن يثبت أنه منطقة مفيدة جدا لدراسة هذه الظاهرة وبائيا ، حيث ثبت وقوعها في العديد من المرضى الجراحيين . إن الإدراج الروتيني لقياس الوزن والطول و بساطة هذا القياس في مرضى المستشفيات قبل إجراء عملياتهم الجراحية يجعل دراسة هذه الظاهرة من قبل طبيب التخدير مسألة متاحة ، و لقد دعيت هذه الظاهرة خطئا ، كما هو المعروف عموما ، باسم "مفارقة البدانة" ، على الرغم من أن التناقض موجود أيضا و ربما حتى أكثر في المرضى الذين يعانون من نقص الوزن .

في **الجزء الثاني** ، أجريت دراستان للتدليل على قيمة إجراء تخطيط صدى القلب باعتبارها أداة قوية في يد طبيب التخدير العامل في القترة المحيطة بالجراحة ، وتطبيق وتفسير توصيات المجتمعات المعنية بتخطيط صدى القلب وأمراض القلب ذات العلاقة بفترة ما حول الجراحة بما في ذلك الجمعية الأوروبية لأمراض القلب ، و الجمعية الأمريكية لتخطيط صدى القلب ، وجمعية أطباء التخدير القلب وعائيين ، و كان من المتوقع ملاحظة الالتزام بهذه التوصيات المبنية على الأدلة السريرية لخفض معدل المضاعفات وتحسين النتائج في فترة ما بعد الجراحة ، أي من نواحي نوعية الحياة والبقاء على قيد الحياة، حيث أن هذه المبادئ التوجيهية تستهدف في المقام الأول إدارة التخدير المحيطة بالجراحة في مدى أبعد من مجرد السماح لإجراء العمليات الجراحية على نحو سلس .

الجزء الأول : مفارقة مؤشر كتلة الجسم

في بداية مجموعة دراساتنا ، درسنا مجموعة من المرضى يبلغ عددها ٥٩٥٠ مريضا يعانون من أمراض الشريان التاجي المعروفة قطعا أو المشتبه في وجودها من حيث وقوع مفارقة مؤشر كتلة الجسم (**الفصل الأول**) . و لقد تمكنا من التحديد

الإيجابي للعلاقة العكسية بين مؤشر كتلة الجسم ومعدل الوفيات على المدى الطويل من جميع الأسباب و من الوفاة القلبية ، بحيث أن الفئات ذوات المعدلات المنخفضة لمؤشر كتلة الجسم تحمل مخاطر أعلى من حيث الوقوع الإجمالي للوفيات أو من الوفيات القلبية على المدى الطويل أكثر من الفئات ذوات مؤشر كتلة الجسم الأعلى .

في **الفصل الثاني** ، أظهرت نتائجنا أن معدل الوفيات انخفض بشكل ملحوظ مع زيادة مؤشر كتلة الجسم في مجموعة من المرضى الذين يعانون أمراض الشرايين المحيطية الذين خضعوا لاختبارات ,وظائف الرئتين قبل إجراء الجراحات الخاصة بهم ، و لقد أظهر التصنيف التحتي الإضافي لمرضانا وفقا لشدة مرض الإنسداد الرئوي المزمن أن المرضى الذين يعانون من نقص الوزن مرتبطين مع صورة أشد من مرض الانسداد الرئوي المزمن .و للمفارقة فقد أدى التصحيح الإحصائي لشدة مرض الإنسداد الرئوي المزمن في التحليل متعدد المتغيرات إلى القضاء على الإرتباط بين المرضى ناقصي الوزن و زيادة الوفيات ، ولكنه لم تبد ثمة فائدة من هذا الإجراء في تعديل ميزة البقاء على قيد الحياة المرتبطة بجماعات المرضى ذوي مؤشر كتلة الجسم الأعلى .

في **الفصل الثالث** ، اختلفت ظاهرة مفارقة مؤشر كتلة الجسم في المدى القصير من المدى الطويل للمتابعة، فعلى الرغم من أن المرضى الذين يعانون من الوزن الزائد دون السمنة أظهروا تحسنا في معدلات البقاء على قيد الحياة في المدى القصير ، مع ذلك ، كان مؤشر كتلة الجسم مرتبطا بشكل متناقض مع طول الإقامة في المستشفى . وقد تبين وجود علاقة عكسية بين مؤشر كتلة الجسم و المعدل الإجمالي للوفيات على المدى الطويل بشكل واضح في هذه الفئة من المرضى. وكشف مزيد من الدراسة حول أسباب الوفيات في المرضى المتوفين أن انخفاض مؤشر كتلة الجسم كان مرتبطا مع وفاة بالسرطان ، في حين تحسنت فرص البقاء على قيد الحياة للمرضى الذين يعانون من زيادة الوزن فقط بالنسبة للأسباب العائدة لأمراض القلب .

وركز **الفصل الرابع** على خطر الإصابة بمرض الأوعية الدموية المحيطية المتعددة والتأثير المحتمل لذلك على مفارقة مؤشر كتلة الجسم . ورغم أن جميع عوامل الخطورة قد استهدفت على قدم المساواة مع العلاج الطبي في جميع الفئات لمؤشر كتلة الجسم ، فإن نقصان الوزن كان خطرا مستقلا لانخفاض فرص البقاء على قيد الحياة ، وأظهر أولئك المرضى أدنى استخدام للعقاقير الواقية للقلب . ومع ذلك ، فإن فئة زائدي الوزن من المرضى أظهرت أعلى نسبة لانتشار مرض أمراض الأوعية الدموية المحيطية المتعددة و كذلك لاستخدام العقاقير الواقية للقلب ، وكانت مرتبطة بتحسن فرص البقاء على قيد الحياة على المدى الطويل ضد جميع أسباب الوفيات ، و لقد وجد أن التفاعل الإحصائي بين تقسيم مؤشر كتلة الجسم ، ووجود مرض الأوعية الدموية المحيطية المتعددة و نتائجها على فرص البقاء على المدى الطويل غير ذي قيمة في هذه الفئة من المرضى .

في **الفصل الخامس** ، أجرينا مراجعة أدبية علمية على "مفارقة البدانة" في مرضى الجراحات العامة . لقد بدا لنا أن المرضى في اقصى معدلات مؤشر كتلة الجسم ، المتضمنين كلا من ذوي نقص الوزن و ذوي السمنة المفرطة لديهم أعلى معدلات الاعتلال والوفيات بعد الجراحات الخطرة ، الأمر الذي لا يزال قائما حتى في المدى البعيد، أما السبب وراء "مفارقة البدانة" فربما يكون متعدد العوامل، وهذا يوفر إمكانية للبحث في المستقبل من أجل تحسين نتائج البقاء بالنسبة للأشخاص في كلا الجانبين القصويين من مؤشر كتلة الجسم الأمثل .

الجزء الثاني : توسيع استخدام تخطيط صدى القلب كأداة مساعدة أثناء و في الفترة المحيطة بالجراحة

تطلب منا هذا الجزء إجراء دراستين ترصديتين . و قد أظهرت الدراسة التي قدمت في **الفصل السادس** معدل أعلى من مظاهر نقص التروية القلبية المحرض من خلال إجراء الإختبار الإجهادي للقلب باتخدام عقار الدوبيوتامين ، أكثر من تلك التي تم الكشف عنها اثناء الجراحة باستخدام تخطيط صدى القلب من خلال تنظير المريء ، مع اتفاق سيء من حيث الموقع بين أماكن نقص تروية عضلة القلب للمرضى االذين خضعوا لإجراء جراحات الأوعية الدموية المحيطية عالية الخطورة . اقترب معدل نقص التروية القلبي تحت الإكلينيكي في هذه الفئة المحدودة من المرضى و التي تم الكشف عنها عن طريق ارتفاع مستويات التروبونين القلبي دون مزيد من مظاهر نقص التروية الأخرى من ١٥% ، في حين بلغ معدل احتشاء عضلة القلب ١١% . و حدث الوفاة قلبية المصدر في ٦% من المرضى . و قد أمكن التنبؤ بحدوث نقصان التروية القلبية أثناء وبعد الجراحة و تشوهات حركية جدار القلب حال الراحة باستخدام الإختبار الإجهادي للقلب باتخدام عقار الدوبيوتامين ، ولكن ذلك لم يكن ممكنا للتنبؤ بمواقع تشوهات الحركية الجدارية الجديدة . و قد كانت نسبة التنبؤ بمواقع الإحتشاء القلبي ١٠٠% في جميع الحالات التي حدث بها احتشاء قلبي بعد الجراحة ، باستخدام تخطيط صدى القلب من خلال تنظير المريء أثناء الجراحة ، في حين أن اختبار الإجهاد القلبي قبل الجراحة لم يتوقع الموقع بشكل صحيح إلا في ثلث الحالات فقط . لقد أضافت هذه الدراسة دليلا مرجحا إلى المصلحة المفترضة للعلاج العام بالعقاقير في مرضى نقصان تروية القلب ، مرجحا إياه على العلاج الإختراقي التدخلي الذي يركز على بعض الفروع التاجية و مهاجمة محددة للآفات الشريانية الجانية لفروع الشريان التاجي قبل جراحة الأوعية الدموية .

وأخيرا، أظهر **الفصل السابع** أن اختلال وظيفة البطين الأيسر هو موجود في نصف المرضى الذين يخضعون لإجراءات الأوعية الدموية المحيطية ، في ٢٠% فقط منهم كانت هناك أعراض ، و الثمانون بالمائة الباقين كانوا بلا أعراض و انقسم اعتلال وظيفة البطين الإيسر بالتساوي بين الخلل الانقباضي والانبساطي . و قد وجد أن الإلتزام بتوصيات جمعية القلب الأوروبية كان فقط في ثلث المرضى متمثلا في العلاج باستخدام مثبطات الإنزيم المحول للأنجيوتنسين أو حاصرات مستقبلاته أو مدرات البول . وأشارت هذه النتائج إلى عدم كفاية علاج هذه المجموعة من المرضى مقارنة مع المبادئ التوجيهية للجمعية أمراض القلب الأوروبية على الرغم من ارتفاع معدل انتشار هذه المشكلة في هذه الفئة من المرضى بعينها .

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As a beginning of who I am, I must mention my late father who passed away at the beginning of my study at Erasmus MC (February 14th 2005). He was the propelling force encouraging me along my whole life. He devoted his life for me and my brothers and he still living inside my beating heart. I was truly blessed to be in the heart and mind of my beloved mother who's prayers, love and care fill my whole life with joy and satisfaction. A word to my beautiful wife: "*you will always remain my genuine only love and sole-mate till death sets us apart. I always see and feel you beautiful"*. To all my children and my brothers: "*you truly made me a lucky man*".

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Beyond the borders of language and culture I lived for a short time in the beautiful Holland; that's what Egyptians usually refer to the Netherlands. All my memories in the Netherlands will stay unforgotten and vivid in my dreams.

Curriculum Vitae

Wael Galal Mohamed Mostafa was born on April 5, 1971 in the city of Tanta, Gharbia governorate, Egypt. He is the middle of three male siblings of a middle-class Egyptian family. His father was a lawyer, and his mother was a French language teacher. He moved during his primary education with his family to Saudi Arabia and completed his secondary education there in 1987. He was nominated the fourth over the whole kingdom in his high-school degree. In 1988, he joined Tanta University Faculty of Medicine, Tanta, Egypt and obtained his bachelor degree in medicine and surgery in November 1994. After completing his training as house officer in 1995, he worked as resident in the anesthesia department at Tanta University Hospitals in the period from 1996 to 1999. During these stormy years of his carreer, he married and got his first child in late 1998. He obtained his Master degree (MSc) in anesthesiology at the end of year 1999. In 2000, he joined the anesthesia department again as an instructor of anesthesiology. Subsequently, his department appointed him as assistant lecturer in 2002. He was nominated for a -joint-supervision scholarship- scientific mission by the Egyptian Ministry of Higher Education for undertaking his doctorate thesis in the Netherlands. He joined the anesthesia department at Erasmus University Medical Centre in January the 7th 2005 as a researcher in anesthesia for the high-risk vascular surgical patients. He returned to Egypt in 2006 and had his doctorate degree (MD) from Tanta Faculty of Medicine in 2007. He got promoted as a faculty staff and lecturer of anesthesiology of his home university. He soon returned to Rotterdam to continue his PhD research program with the anesthesia department at Erasmus MC. He is currently working as a consultant of anesthesia, King Fahad Hospital, Al-Baha, Kingdom of Saudi Arabia after since June 2009. In 2012, he became the director of Saudi Anesthesia Board training program in Al-Baha, and an anesthesia trainer at the Saudi Commission for Health specialties (SCFHS). His research studies along with his PhD training continued under the supervision of prof. dr. Robert Jan Stolker and prof. dr. Hence J M Verhagen.

Publication List

1. Galal W, Valentijn TM1, Tjeertes EK, Hoeks SE, Verhagen HJ, Stolker RJ. The obesity paradox in the surgical population. Surgeon. 2013; 11(3): 169-76

2. Galal W, Valentijn TM1, Hoeks SE, van Gestel YR, Verhagen HJ, Stolker RJ. Impact of obesity on postoperative and long-term outcomes in a general surgery population: a retrospective cohort study. World J Surg. 2013; 37(11): 2561-8

3. van Kuijk JP, Flu WJ, Galal W, Chonchol M, Goei D, Verhagen HJ, Bax JJ, Poldermans D.The influence of polyvascular disease on the obesity paradox in vascular surgery patients.
J Vasc Surg. 2011 Feb;53(2):399-406.

4. Galal W, Hoeks SE, Flu WJ, van Kuijk JP, Goei D, Galema T, den Uil C, van Gestel YR, Bax JJ, Verhagen HJ, Poldermans D. Relation between preoperative and intraoperative new wall motion abnormalities in vascular surgery patients: a transesophageal echocardiographic study. Anesthesiology. 2010 Mar;112(3):557-66.

5. Flu WJ, van Kuijk JP, Galal W, Kuiper R, van de Ven LL, Verhagen HJ, Bax JJ, Poldermans D. Prevalence and pharmacological treatment of left-ventricular dysfunction in patients undergoing vascular surgery. Eur J Heart Fail. 2010 Mar;12(3):288-93.

6. Goei D, Flu WJ, Hoeks SE, Galal W, Dunkelgrun M, Boersma E, Kuijper R, van Kuijk JP, Winkel TA, Schouten O, Bax JJ, Poldermans D. The interrelationship between preoperative anemia and N-terminal pro-B-type natriuretic peptide: the effect on predicting postoperative cardiac outcome in vascular surgery patients. Anesth Analg. 2009 Nov;109(5):1403-8.

7. van Kuijk JP, Dunkelgrun M, Schreiner F, Flu WJ, Galal W, van Domburg RT, Hoeks SE, van Gestel YR, Bax JJ, Poldermans D. Preoperative oral glucose tolerance testing

in vascular surgery patients: long-term cardiovascular outcome. Am Heart J. 2009 May;157(5):919-25.

8. Galal W., Van Gestel YRBM., Hoeks SE., Sin DD., Bax JJ., Verhagen HJM., Awara AMM., Klein J., Van Domburg RT., Poldermans D. The obesity paradox in patients with peripheral arterial disease: The influence of chronic obstructive pulmonary disease. Submitted to Chest in February 2008 (accepted in Chest – first appeared online July 18th 2007).

9. Galal W, van Domburg RT, Feringa HH, Schouten O, Elhendy A, Bax JJ, Awara AM, Klein J, Poldermans D. Relation of body mass index to outcome in patients with known or suspected coronary artery disease. Am J Cardiol. 2007 Jun 1;99(11):1485-90.

10. Feringa HH, Bax JJ, Boersma E, Kertai MD, Meij SH, Galal W, Schouten O, Thomson IR, Klootwijk P, van Sambeek MR, Klein J, Poldermans D. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. Circulation. 2006 Jul 4;114(1 Suppl):I344-9.

11. Feringa HH, van Waning VH, Bax JJ, Elhendy A, Boersma E, Schouten O, Galal W, Vidakovic RV, Tangelder MJ, Poldermans D. Cardioprotective medication is associated with improved survival in patients with peripheral arterial disease. J Am Coll Cardiol. 2006 Mar 21;47(6):1182-7.

PhD Portfolio

Name of PhD student: **Wael Galal Mohamed Mostafa**	PhD period: **2005-2016**	
Erasmus MC Department: **Anesthesiology**	Promoter(s): **prof dr. Robert Jan Stolker** **prof dr. Hence J M Verhagen**	
Research School: **Erasmus MC**	Supervisor: **prof dr. Robert Jan Stolker** **prof dr. Hence J M Verhagen**	
1. PhD training		
	Year	**Workload (ECTS)**
General courses		
International Test of English as a Foreign Language (TOEFL) (AMEDEAST Co. LTD, Cairo, EGYPT)	2004	3
International computer driving license (ICDL)	2004	2.1
Developing spreadsheets with Microsoft Excel	2004	1.5
Writing in scientific English for researchers	2004	2.1
Prerequisites of leadership; Helwan Center for Preparing Leaders, Helwan, Cairo, Egypt	2004	1.5
Transesophageal echocardiography; basic principles (the outpatient clinic of Thoraxcenter, Erasmus MC)	2005	3
Transesophageal echocardiography; (Cardiac surgery theatre, Thoraxcenter, Erasmus MC)	2005	3
Specific courses		
Advanced life support provider	2004	0.9
Advanced life support provider	2006	0.9
Advanced life support provider	2010	0.9
Advanced life support provider	2015	0.9
Generic instructor course (Cairo University, Egypt)	2007	1.2
Train the trainer (TOT) in anesthesia simulation	2014	0.9
Seminars and workshops		
Advanced airway management	2008	0.9
Ultrasound-guided central venous access and regional anesthesia	2009	0.9
Hands-on workshop on ultrasound-guided peripheral nerve blocks and central venous access, King Fahad Military Hospital, Jeddah	2013	1.2
Workshop on anesthesia simulation	2014	0.6
Presentations		
Erasmus MC anesthesiology department week seminar lecture:- - The obesity paradox in coronary artery disease patients	2006	0.3
National Egyptian conferences	2007-2010	1.2
The European Society of Cardiology Congress (ESC), annual	2006-2009	1.2
2x Poster presentations at the European Society of Cardiology Congress (ESC), 2010	2010	0.6
Egyptian central society congress in anesthesia, critical care and pain management, annual	2000-2012	3
National conferences in Saudi Arabia	2009-2015	1.5
Presentation in front of the Western Saudi Province regional committee for anesthesia: Formation of the first Saudi National anesthesia database	2013	0.3
2. Teaching		
	Year	**Workload (ECTS)**
• Lecturing		

Conscious sedation courses [lecturing on pharmacology, risk reduction during sedation & practical skill stations (quarterly performed courses)	2009-2016	1.2
Acute postoperative pain management in adults [one lecture] (quarterly performed courses)	2009-2016	1.2
Modifying the risks of perioperative blood transfusion	2010, 2013	0.3
Guidelines for perioperative cardiovascular management of cardiac patients undergoing non-cardiac surgery	2012, 2015	0.3
• Supervising		
Anesthesia MSc students in Tanta faculty of medicine, Egypt	2007-2009	1.5
The Saudi Anesthesia Board program students (R1-R5)	2012-2016	3
TOTAL (ECTs)		35.7

Stellingen

(PROPOSITIONS)

Behorende bij dit proefschrift

(Belonging to the thesis)

The Obesity Paradox in Surgical Patients: From Preoperative Assessment to Long-Term Outcome

By; Wael Galal Mohamed Mostafa
Rotterdam, The Netherlands; 2016

1. The phenomenon of inverse relationship between body mass index and mortality is currently observed in patients with peripheral arterial disease and coronary artery disease undergoing vascular surgery as well as in other general surgical population. (own thesis)

2. In the overweight and obese groups, patients appear relatively better targeted in modern societies with therapeutic measures correcting cardiovascular risk factors and the association with mortality from cardiovascular causes is modified. (own thesis)

3. A higher prevalence of more severe forms of life-threatening chronic diseases is present among underweight patients which requires more vigilant attention. (own thesis)

4. In cardiac patients undergoing non-cardiac surgery, preoperative pharmacologic stress testing can predict which patients are at risk for the occurrence of intraoperative and postoperative myocardial ischemia and infarction but not the location of such predicted ischemia. This is better correlated with intraoperative transesophageal echocardiography. (own thesis)

5. Underestimation of the prevalence of left ventricular dysfunction in peripheral arterial disease patients might require routine implementation of preoperative echocardiography prior to vascular surgery. (own thesis)

6. The combination of modern medicine and social life have undoubtedly caused the extension in both human expectation and bodily mass.

7. If current trends continue, obesity will soon overtake cigarette smoking as the leading cause of preventable death in the United States. (Carl J. Lavie, Hector O. Ventura and Richard V. Milani, Chest 2008 Nov;134(5):896-8)

8. The high rate of perioperative cardiac deaths, myocardial ischemia and infarction, and sub-clinical ischemia in cardiac patients who underwent non-cardiac surgeries raise the question to escalate the utility of intraoperative TEE in the ESC recommendations.

9. The disconnection between the severity of anatomic obstruction and the MI risk is one of the main pieces of evidence that plaque rupture depends on its composition rather than on its size. (Balachundhar Subramaniam; Anesthesiology 2010 Mar;112(3):524-6)

10. Intensive medical anti-ischemic therapy is superior to focused therapeutic coronary interventions aiming at improving coronary perfusion in patients with ischemic heart disease prior to major non-cardiac surgery. (*Reflections from* McFalls EO et al. NEJM 2004; 351 2795-804; and Garcia S et al. JACC 2008; 102: 809-813)

11. Modern communities now clearly understand the risks associated with excessive weight loss and weight gain. It is not strange that more European countries ban excessively underweight “cat-walk” fashion models. (The Guardian, BBC and Time; April the 3rd 2015)