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PERIPROCEDURAL PROGNOSTIC FACTORS IN CORONARY INTERVENTIONS - RETROSPECTIVE STUDIES

Jarmo Gunn

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To my greatest achievements: Verneri, Iiris and Artturi

ABSTRACT

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Periprocedural prognostic factors in coronary interventions – retrospective studies

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Background: Approximately 11,000 revascularization procedures, either percutaneous coronary interventions (PCI) or coronary artery bypass grafting surgery (CABG), are performed yearly in Finland for coronary artery disease. Periprocedural risk factors for mortality and morbidity as well as long-term outcome have been extensively studied in general populations undergoing revascularization. Treatment choice between PCI and CABG in many high risk groups and risk-stratification, however, needs clarification and there is still room for improvement in periprocedural outcomes.

Materials and methods: Cohorts of patients from Finnish hospitals revascularized between 2001 and 2011 were retrospectively analyzed. Patient records were reviewed for baseline variables and postprocedural outcomes (stroke, myocardial infarction, quality of life measured by the EQ-5D –questionnaire, repeat revascularization, bleeding episodes). Data on date and mode of death was acquired from Statistics Finland. Statistical analysis was performed to identify predictors of adverse events and compare procedures.

Results: Postoperative administration of blood products (red blood cells, fresh frozen plasma, platelets) after isolated CABG independently and dose-dependently increases the risk of stroke. Patients 80 years or older who underwent CABG had better survival at 5 years compared to those who underwent PCI. After adjusting for baseline differences survival was similar. Patients on oral anticoagulation (OAC) for atrial fibrillation (AF) treated with CABG had better survival and overall outcome at 3 years compared to PCI patients. There was no difference in incidence of stroke or bleeding episodes. Differences in outcome remained significant after adjusting for propensity score. Lower health-related quality of life (HRQOL) scores as measured by the visual analogue scale (VAS) of the EQ-5D questionnaire at 6 months after CABG predicted later major adverse cardiac and cerebrovascular events (MACCE). Deteriorating function and VAS scores between 0 and 6 months on the EQ-5D also independently predicted later MACCE.

Conclusions: Administration of blood products can increase the risk of stroke after CABG and liberal use of transfusions should be avoided. In the frail subpopulations of patients on OAC and octogenarians CABG appears to offer superior long-term outcome as compared to PCI. Deteriorating HRQOL scores predict later adverse events after CABG.

Keywords: percutaneous coronary intervention, coronary artery bypass grafting, age over 80, transfusion, anticoagulants, coronary artery disease, health-related quality of life, outcome.

TIIVISTELMÄ

Jarmo Gunn

Sepelvaltimotoimenpiteiden ennusteelliset tekijät – retrospektiivisiä tutkimuksia

Kirurgian oppiaine, Turun Yliopisto ja Sydänkeskus, Turun Yliopistollinen Keskussairaala, Turku, Suomi
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Tausta: Suomessa tehdään vuosittain yli 10 000 sepelvaltimoiden pallolaajennusta (PCI) ja ohitusleikkausta (CABG). Toimenpiteeseen liittyviä riskitekijöitä ja pitkäaikaisennustetta on tutkittu laajalti tavanomaisissa potilasaineistoissa. Toimenpidevalintaa ohjaavaa tietoa riskiryhmistä sekä riskinarviointikeinoja kuitenkin tarvitaan yhä ja välittömiä toimenpiteen jälkeisiä tuloksia voi edelleenkin parantaa.

Aineisto ja menetelmät: Vuosien 2001 ja 2011 välillä suomalaisissa sairaaloissa sepelvaltimoihin kohdistuvin toimenpitein hoidettuja potilaskohortteja tutkittiin taannehtivasti. Potilasasiakirjoista etsittiin toimenpidettä edeltävät sairastavuustiedot, toimenpidejakson tiedot sekä toimenpiteen jälkeisen ajan tiedot (aivo- ja sydäninfarktit, uusintatoimenpiteet, verenvuodot ja EQ-5D –lomakkeella mitattu elämänlaatu). Kuolintiedot haettiin Tilastokeskuksen rekistereistä. Tilastomatemaattisin keinoin selvitettiin myöhäissairastavuutta ja -kuolleisuutta ennakoivat tekijät ja toimenpideryhmien väliset erot.

Tulokset: Leikkauksen jälkeinen verituotteiden (punasolut, jääplasma, verihiutaleet) annostelu lisää annosriippuvaisesti ja itsenäisesti toimenpiteen jälkeisen aivoinfarktin riskiä. Yli 80-vuotiaat sepelvaltimotoimenpitein hoidetut potilaat ovat todennäköisemmin elossa ohitusleikkauksen kuin pallolaajennuksen jälkeen 5 vuoden seuranta-aikana. Lähtötilanteen muuttujien samankaltaistamisen jälkeen ei tullut esille eroa ryhmien välillä. Eteisvärinän vuoksi antikoaguloitujen potilaiden elossaolo ja haittatapahtuman todennäköisyys ovat paremmat ohitusleikkauksen jälkeen. Aivoinfarkteissa tai verenvuodoissa ei ollut eroa ryhmien välillä. Tulos säilyy propensity score -korjauksen jälkeen. Huonompi visual analogue scale (VAS) -arvo EQ-5D -lomakkeella mitattuna 6 kk CABG:n jälkeen ennakoi haittatapahtumia. Huononeva VAS ja toimintakyky EQ-5D -lomakkeella mitattuna ennakoivat myöhempiä haittatapahtumia.

Johtopäätökset: Verituotteiden anto ohitusleikkauksen jälkeen lisää aivoinfarktin riskiä ja sitä tulisi pyrkiä välttämään. Tutkituissa suuren riskin potilasryhmissä (yli 80-vuotiaat ja eteisvärinän vuoksi antikoaguloidut) ennuste vaikutti paremmalta sepelvaltimoiden ohitusleikkauksen kuin pallolaajennuksen jälkeen. Huononeva elämänlaatu EQ-5D -mittarilla arvioituna ennustaa ohitusleikkauksen jälkeisiä haittatapahtumia.

Avainsanat: sepelvaltimoiden katetritoimenpide, sepelvaltimoiden ohitusleikkaus, ikä yli 80 vuotta, verensiirto, antikoagulaatio, sepelvaltimotauti, terveyspainotteinen elämänlaatu, ennuste

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ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute coronary syndrome
ADL	Activities of daily living
AF	Atrial Fibrillation
AHA	American Heart Association
AMI	Acute myocardial infarction
ASA	Acetylsalicylic acid a.k.a. aspirin
ASCERT	ACCF and STS Database Collaboration on the Comparative Effectiveness of Revascularization Strategies -study
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CART	Classification and regression tree (also known as binary recursive partitioning)
CHD	Coronary heart disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation study
DES	Drug eluting stent
EACTS	European Association for Cardio-Thoracic Surgery
EF	Ejection fraction
ESC	European Society of Cardiology
FAME	Fractional flow reserve (FFR) vs. Angiography in Multivessel Evaluation trial
FFR	Fractional flow reserve
FREEDOM	Future REvascularization Evaluation in patients with Diabetes mellitus trial
HR	Hazard ratio
HRQOL	Health related quality of life
IHD	Ischemic heart disease

INR	International normalized ratio
LAD	Left anterior descending coronary artery
LIMA	Left internal mammary artery
LITA	Left internal thoracic artery
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
MACCE	Major adverse cardiac and cerebrovascular event
NSTEMI	Non ST -segment elevation myocardial infarction
OAC	Oral anticoagulation
OR	Odds ratio
PCI	Percutaneous coronary intervention
QOL	Quality of life
RBC	Red blood cell
STEMI	ST -segment elevation myocardial infarction
STS	Society of Thoracic Surgeons
SYNTAX	SYNergy between PCI with TAXUS and Cardiac Surgery -trial
TIA	Transient ischemic attack
UAP	Unstable angina pectoris
VAS	Visual analogue scale

LIST OF ORIGINAL PUBLICATIONS

I. Mikkola R, **Gunn J**, Heikkinen J, Wistbacka JO, Teittinen K, Kuttila K, Lahtinen J, Juvonen T, Airaksinen JK, Biancari F. Use of blood products and risk of stroke after coronary artery bypass surgery. Blood Transfus. 2012 Oct;10(4):490-501.

II. **Gunn J**, Kuttila K, Vasques F, Virtanen R, Lahti A, Airaksinen J, Biancari F.Comparison of results of coronary artery bypass grafting versus percutaneous coronary intervention in octogenarians. American Journal of Cardiology. 2012 Oct 15;110(8):1125-9.

III. **Gunn JM**, Kuttila KT, Kiviniemi TO, Biancari F, Ylitalo A, Airaksinen KE. Coronary artery bypass surgery and percutaneous coronary intervention in patients with atrial fibrillation and oral anticoagulation. *Accepted for publication in the Annals of Medicine on March 8th 2014.*

IV. **Gunn JM**, Lautamäki AK, Hirvonen J, Kuttila KT. The prognostic significance of declining health related quality of life scores at 6 months after coronary artery bypass surgery. QJM 2014 May;107(5):369-74.

1. INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in the world in general (Lopez et al 2001) and in Finland in particular (Statistics Finland). In the 1960s Finland had the highest mortality in the world due to CAD (Vartiainen et al 2010). Since then the mortality has sharply decreased owing greatly to an improvement in risk factor profiles (Ford et al 2007, Vartiainen et al 2000 and 2010). Despite the declining mortality there were still 11767 deaths in Finland in 2010 due to ischemic heart disease accounting for 23,1 % of the overall mortality (Statistics Finland).

The reduction of mortality combined with an overall increase in incidence mirrors a changing pattern of CAD; acute ST elevation myocardial infarction is decreasing in incidence and myocardial infarctions in general are less often fatal (Krumholz et al 2009, McManus et al 2011, Movahed et al 2009, Schmidt et al 2012, Smolina et al 2012). The encouraging progress made in mortality is offset by an increasing incidence of cardiovascular disease (Ford et al 2007, Kattainen et al 2006).

The socioeconomic burden caused by CAD remains substantial; out of 5 400 519 Finns (Väestörekisterikeskus, accessed 30.11.2011) 186 687 were on medication for chronic coronary artery disease (KELA, Kelasto-database 2011, accessed 27.6.2012) with a 254 360 699 euros/year expenditure for cardiovascular medication alone. Even as progress has been made, mortality for acute coronary syndromes still remains high (Nikus et al 2007). The need for invasive diagnostics and treatment is considerable and growing. This can be seen in Finland as 23 000 coronary angiograms, almost 9 000 percutaneous coronary interventions and over 2000 coronary artery bypass operations were performed in 2010 (Mustonen et al 2011).

Coronary heart disease is a process that begins in childhood and progresses into manifest disease over several decades' time (McGill et al 2000). The incidence at a population level can be explained to a large extent by several known risk factors identified already in 1961 in the pivotal Framingham study (Kannel et al 1961), many of these factors have been verified time and again and many have been found modifiable as well as predictive of progression (Batsis et al 2010, DeFilippis et al 2011, Lopez et al 2001, and Yusuf et al 2004). Some major risk factors (e.g. alcohol consumption, tobacco smoking) can be regulated by legislative and educational measures effectively, while others such as obesity are increasing in prevalence despite growing concern and efforts (Berghöfer et al 2008, Kautiainen et al 2002) . Several contributing factors such as elevated blood pressure, diabetes and high cholesterol can be managed medically and the mortality of patients who are known to be at risk can be reduced with optimal treatment (Capewell et al 2010). Coordinated changes in nationwide policy have proven highly effective at least in Finland as proven by an 85% reduction in coronary heart disease with the implementation of the interventional measures adopted from the North Karelia Project

(Vartiainen et al 2010). This highlights the effectiveness of a concerted primary and secondary prevention endeavour by the public and private sectors, non-governmental organizations and policy-makers (Pietinen et al 1988, Puska et al 2010 and Salonen et al 1989).

Between 1980 and 2000 of the 47 % reduction in mortality for patients with CAD related to treatment, 5 % could be attributed to coronary revascularization for chronic angina and 10 % to initial treatment of acute coronary syndromes (myocardial infarction and unstable angina) (Ford et al 2007). Secondary prevention and management of population level risks are thus of paramount importance for the general public. For the individual patient for whom the risk has actualized, the value of invasive treatment and possible interventions, however, becomes vital. Although there is solid data in a general CAD population on the risk factors influencing choice and outcome of invasive treatment (Nashef et al 2012, Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery 2010), it is equally well known that patient specific set (age, sex, comorbidities) (Nashef et al 2012) and modifiable characteristics (periprocedural medication and treatment, lifestyle, specific techniqual aspects such as choice of implant and grafts) (Griffo et al 2013, Lytle et al 2004) may largely alter the picture.

These studies focused on the the periprocedural choices of treatment and their impact on the outcome of patients in need of coronary revascularization. Additionally, these studies aim to identify clinically applicable predictors of later adverse outcome.

2. REVIEW OF THE LITERATURE

2.1 Invasive treatment of coronary artery disease

2.1.1 History of coronary artery bypass grafting (CABG)

Alexis Carrel, a French surgeon and biologist, is widely accepted as the first to describe the principles required for coronary artery bypass grafting. He was awarded the Nobel prize in Physiology or Medicine in 1912 for his work (Carrel 1910). Carrel, however, lacked many key technical advances required to support the clinical application of his methods, and it was not until the late 1940s to early 1960s that several pioneers like Vineberg in Canada (Vineberg 1949), Kolesov in the USSR (Kolesov et al 1965) and DeBakey as well as Garret (Garrett et al 1973) in the United States started experimenting on human subjects. The first successful coronary artery bypass operation in a human patient was done by Robert Goetz in 1960 (Konstantinov 2000). The first CABG program is credited to Favaloro in Cleveland, USA, starting with saphenous aortocoronary grafting in 1967 (Favaloro 1969). In the 1970s and 1980s, several landmark studies (European Coronary Surgery Study Group 1982, Takaro et al 1976 and The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group 1984), most notably CASS (CASS investigators 1984), described the effectiveness of CABG especially compared to medical treatment and essentially delineated the indications for invasive treatment of CAD. The use of the left internal mammary artery (LIMA or LITA, left internal thoracic artery) as graft to the left anterior was first performed by Kolesov and popularized in the west by Green (Green et al 1970). Already in the 1980s patency rates over 10 years of up to 90% were reported with LIMA -grafts, and a survival benefit as compared to saphenous vein grafts in the 1990s consequently entailing the nearly universal adoption of the LIMA as the primary graft usually on the left anterior descending coronary artery (LAD) (Cameron et al 1996, Loop et al 1986 and Lytle et al 1985). The most frequently used secondary graft in coronary surgery is the great saphenous vein (*lat.: vena saphena magna*) mainly due to the ease of its harvesting and usually sufficient available length. Its patency, however, is considered inferior to arterial grafts (e.g. radial artery, right internal mammary artery) in many studies (Bartnes 2013, Kurlansky et al 2010 and Lytle et al 2004), although several recent studies have shown good results with careful harvesting techniques and postoperative care (Hayward et al 2010, Johansson et al 2010) and it appears that the technique used for vein harvesting is an important determinant of vein graft patency (Dashwood et al 2007 and 2009, Ouzounian et al 2010, Parang et al 2009 and Soyombo et al 1993). There are, however, several studies showing a survival benefit in the long term with arterial grafts over saphenous veins as secondary grafts (Locker et al 2012, Pick et al 1997, Taggart et al 2001a and Zacharias et al 2004).

2.1.2 History of percutaneous coronary interventions (PCI)

The prerequisite for percutaneous coronary interventions was the technique of selective coronary angiography, accredited to Charles Dotter, an American radiologist often referred to by the monicker “Father of interventional radiology”. Dotter was the first to treat arterial stenosis by remodelling the artery with a catheter based approach in a patient with lower limb ischemia and reported the results in 1964, calling his technique transluminal angioplasty (Dotter et al 1964). Balloon angioplasty of peripheral arterial lesions was performed by Grüntzig in 1974 and in coronary arteries in 1977 (Grüntzig et al 1979) leading to the emergence of interventional cardiology. Balloon angioplasty was associated with a risk of abrupt closure and restenosis of the treated vessel and subsequently there was a surge in development leading to the refinement of percutaneous techniques. For example the Gianturco-Roubin (Steenkiste et al 1991) and Palmaz-Schatz (Schatz et al 1991) coronary stents were introduced in the 1990’s showing a lower risk of abrupt closure and restenosis as compared to angioplasty alone leading to widespread adoption of intracoronary stenting. (Fischman et al 1994, Hearn et al 1993 and Serruys et al 1994). Instent restenosis has been recognized as a factor affecting long term outcome and has been greatly reduced with the introduction of drug eluting stents (DES) (Rensing et al 2001). Although the incidence of restenosis has been reduced, stent thrombosis remains an issue. This is a phenomenon related exclusively to stenting, but coronary bypass grafts are also prone to occlusion although this appears to translate into less clinical evidence (Farooq et al 2013b).

2.1.3 Contemporary rationale for invasive treatment of coronary artery disease

The rationale behind indications for modern invasive treatment of stenotic or obstructed coronaries was widely accepted after Gould and Lipscomb described the effect of luminal narrowing on blood flow in a dog model in 1974 (Gould et al 1974a and 1974b). They showed that a 50 % reduction in diameter impaired maximal vasodilation and a narrowing of 85 % or more resulted in impaired blood flow at rest (Gould et al 1974a and 1974b). This translates clinically into the generally accepted thresholds of significance of maximal anatomical narrowing of vessel diameter as seen on the coronary angiography of 50% or more in the left mainstem coronary artery or 70% or more in an epicardial location. In general, however, stable angina pectoris or stable CAD, is treated primarily with a conservative approach (Fihn et al 2012). In other words most of these patients are deemed at a relatively low risk for complications and treated with optimal medical therapy and lifestyle counselling. The most compelling basis for this is the COURAGE-study, which as a summary showed that treating stable CAD routinely with PCI confers no benefit to patients (Boden et al 2007, Teo et al 2009). It was, however, previously shown that a functional approach to coronary lesions might be beneficial, i.e. targeting only stenoses that are significant on pressure guidewire measurement on coronary angiography (based on Fractional Flow Reserve, FFR) and not only significant based on visual assessment (Pijls et al 2007). Consequently the FAME 2 study was launched in order to compare optimal medical treatment and FFR -guided PCI in patients with stable CAD (De Bruyne et al 2012). The study was stopped short due to the considerable 8-fold difference in emergent revascularization in favour of the PCI -treated group. These results corroborate that inducibility and extent of ischemia are the drivers of outcome in stable disease (Metz et al 2007). It has recently been proposed that an FFR-guided approach to coronary surgery might also be useful (Toth et al 2013).

Acute manifestations of coronary artery disease, i.e. so called acute coronary syndromes (ACS), namely unstable angina pectoris (UAP), non-ST -segment elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) are potentially life-threatening emergencies and restoration of blood flow is promptly needed; in-hospital mortality rates are 3% for UAP, 6% for NSTEMI and 7% for STEMI (Steg et al 2002). In ACS and STEMI the benefit of early revascularization in general is regarded unequivocal as demonstrated by both the American College of Cardiology/ American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines on treatment of these conditions (Antman et al 2008, Braunwald et al 2000 and Hamm et al 2011) although the specific strategies are under constant investigation and debate. The choice and timing of revascularization is complicated by several factors: the extent and severity of coronary involvement (PCI or CABG preferred), the hemodynamic stability of the patient (*ad hoc* PCI needed or not) and a myriad of other case-specific issues. As a crude simplification, however, hemodynamically compromising culprit lesions are treated with immediate PCI and definitive treatment mirrors the management of stable coronary disease, i.e. lesion anatomy dictates the choice of revascularization (Fihn et al 2012).

At the time of this study, the most recent guidelines for treatment of stable coronary artery disease are from 2012 by the ACC/AHA (Fihn et al 2012), and the ESC guidelines for myocardial revascularization are from 2010 (Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery EACTS 2010). These guidelines and clinical practice are further supported by evidence from older (Pocock et al 1995) and newer large randomized (most notably the SYNTAX study) and non-randomized studies (ASCERT, FREEDOM) (Weintraub et al 2012, Farkouh et al 2012). 5-year results from SYNTAX show that CABG remains the first choice for complex coronary artery disease and complex left main and PCI is valid in cases of less complicated lesion anatomy (Mohr et al 2013). ASCERT was a study comparing PCI and CABG in a retrospective registry setting encompassing 86,244 isolated coronary artery bypass grafting patients aged ≥65 years and 103,549 patients who underwent PCI (Weintraub et al 2012). Propensity score matching was used to overcome baseline differences. ASCERT showed that in stable angina CABG confers a survival benefit in multivessel disease. Results for the FREEDOM trial (Farkouh et al 2012) were in line with older studies concerning diabetics, such as for example BARI (BARI investigators 1996 and 2007, Feit et al 2000), CABRI (Kurbaan et al 2001) and EAST (King et al 2000). FREEDOM enrolled 1900 patients with diabetes and coronary artery disease, a majority of whom had three-vessel disease, to treatment with CABG surgery or PCI with sirolimus-eluting and paclitaxel-eluting stents.At 5-years follow-up freedom from the primary endpoint as well as survival were better for the CABG group again indicating that CABG is still the primary choice for diabetics with CAD (Farkouh et al 2012).

2.2 Postprocedural outcomes and risk factors

There are a multitude of more and less pertinent outcomes that can be used to measure the success of coronary revascularization or any other invasive treatment. This study focuses on only a few outcomes and their risk factors and predictors, with the main interest being on postprocedural stroke, bleeding, quality of life and survival.

2.2.1 Age

Age is a significant predictor of adverse outcome and mortality in a multitude of diseases at both ends of the spectrum. Although the elderly are generally considered at risk for adverse outcomes, at least in CAD young age can be a predictor of poor outcome possibly due to a more aggressive disease and important baseline morbidity as well as suboptimal adherence to treatment and counseling (Biancari et al 2014).

Old age often comes with increasing comorbidities and in itself is a risk factor (Turrentine et al 2006), but it is becoming apparent that age alone is not the driver of survival even in the very old as demonstrated by research (Abel et al 2013, Leahy et al 2005, Markar et al 2013, Santarpino et al 2013). Advancing age naturally entails a diminishing life expectancy, although for example the life expectancy for octogenarians ceases to diminish as quickly as before 80 years of age alluding to a considerable diversity in general health in this age group (Statistics Finland, Social Security Administration USA). Frailty, characterized by deficits in functioning, such as slow movement and impairments in the activities of daily living (ADL), has been demonstrated to be an important predictor of survival in the elderly in general as well as in old people with cardiovascular disease or interventions (Bravell et al 2008, Ekerstad et al 2011, Fries et al 2005, Klein et al 2005, Partridge et al 2012, Sirola et al 2011).

Elderly patients are a growing population in Western countries and the projected worldwide estimate for increase in this age group between 2000 and 2050 is 5.5-fold amounting to almost 400 million people (United Nations). Taking into consideration that increasing age means increasing prevalence of coronary artery disease and acute coronary syndromes as well as the overall increase in prevalence of cardiovascular disease, this population of octogenarians will make up a large body of patients referred for revascularization (British Heart Foundation 2010, Ford et al 2007, Kattainen et al 2006, Krumholz et al 2009, Movahed et al 2009).

2.2.2 Atrial fibrillation

Atrial fibrillation (AF) is a supraventricular heart rhythm abnormality characterized by very rapid atrial frequency and irregular ventricular contraction activity due to fluctuation of atrioventricular electrical impulse conduction (Raatikainen and Huikuri 2008). Typical electrocardiogram findings are an uneven baseline and indistinguishable normal P -waves.

Atrial fibrillation is the most commonly encountered arrhythmia in clinical practice and it is estimated that 1 in 4 persons will develop AF during their lifetime after 40 years of age (Lloyd-Jones et al 2004). It is estimated that the incidence of AF will double in the United States by 2050 and in the European Union from 2010 to 2060 (Benjamin et al 1998, Go et al 2001 and Krijthe et al 2013). AF in a general population is a risk factor for mortality accounting for a 50-90% increase in deaths (Benjamin et al 1998, Mehta et al 2003) and a well described cause of cerebrovascular events such as stroke and transient ischemic attack (TIA) (Hart et al 2000 and 2003).

Postoperative AF after cardiac surgery is present in 5.5% to 57% (Buffolo et al 1996, Helgadottir 2012 and Patti et al 2006) and has been identified as a risk factor for poorer survival and stroke after CABG (Ad et al 2009, Attaran et al 2011, Biancari et al 2011, Helgadottir et al 2012, Fukahara et al 2010, Lahtinen et al 2004 and Villareal et al 2004). AF has also been shown to have a negative impact on prognosis after PCI (Kinjo et al 2003, Lopes et al 2009 and Ruiz-Nodar et al 2009,).

In patients undergoing coronary revascularization, AF is present preprocedurally in approximately 5% of patients (Ad et al 2009, Attaran et al 2011, Fukahara et al 2010, Lopes et al 2009 and Rubboli et al 2009). The presence of preprocedural AF has also been identified as a harbinger of diminished survival postprocedurally (Ad et al 2009, Attaran et al 2011, Biancari et al 2010, Fukahara et al 2010, Kinjo et al 2003 and Ngaage et al 2007). There has been thus far a paucity of comparative data between PCI and CABG in patients on oral anticoagulation (OAC).

2.2.3 Bleeding

Bleeding events after coronary interventions occur with varying severity after coronary interventions (Herman et al 2010, Ndrepepa et al 2014). Serious bleedings such as intracranial and fatal bleeds are immediately catastrophic, but minor bleeding episodes have a negative impact on prognosis as well after both conservative and interventional treatment (Eikelboom et al 2006, Spencer et al 2007, Yoon et al 2013). Several antithrombotic drugs are in routine use periprocedurally in coronary interventions and are associated with more or less significant risks of bleeding events; aspirin (acetylsalicylic acid a.k.a. ASA) and thienopyridines (P2Y12 –inhibitors) are used to prevent stent thrombosis after PCI or as secondary prevention after ACS (Tanguay et al 2013) and are consequently common also in patients undergoing CABG with recently deployed stents.

2.2.3.1 Warfarin

It is estimated that about 6% of patients undergoing revascularization are on OAC with warfarin (Serruys et al 2009, Tanaka 2012). Warfarin is a widely used anticoagulant. Its mechanism of action is the inhibition of vitamin K -dependent synthesis of calcium dependent clotting factors II, VII, IX and X as well as regulatory proteins C, S and Z resulting in inhibited red blood cell (RBC) aggregation and effectiveness especially in settings of low blood flow (Ansell et al 2008). Warfarin is a slow acting drug with a relatively long half-life and a somewhat narrow therapeutic window. Consequently warfarin requires regular monitoring through blood sampling to maintain an optimal anticoagulation level as measured by the international normalized ratio (INR) (Freedman et al 1992). Warfarin is an important risk factor for bleeding episodes, which is an inevitable side effect of its desired action, i.e. anticoagulation for prevention of thromboembolic complications such as stroke. Reports on bleeding episodes related to warfarin in noninterventional populations vary from 4.7-16.5/100 person years for all bleeding episodes (DiMarco et al 2005, Hylek et al 2007, Palareti et al 1996, van der Meer et al 1993) to 0.45-0.47/100 person years for intracranial hemorrhages (Go et al 2001 and 2003, Palareti et al 1996). Variations in reporting of all bleeding events are probably mostly due to differences in definition of bleeding and accuracy of registry data especially in retrospective studies (Go et al 2003).

Incidence of late bleeding after PCI in patients on warfarin has been reported between 7.5% and 12.3% (Annala et al 2012, Karjalainen et al 2007, Orford et al 2004, Ruiz-Nodar et al 2009). DeWilde et al (2013) reported 1-year bleeding rates of 19.4% and 44.4% after PCI for patients on OAC and clopidogrel and patients with triple therapy (OAC+clopidogrel+aspirin) respectively. Up to one half of bleeding episodes are fatal on triple therapy (rogacka et al 2008). Coronary surgery has been shown to be relatively safe during OAC (Airaksinen et al 2011, Biancari et al 2010), but data on later bleeding outcomes are lacking.

2.2.3.1 P2Y12 -inhibitors

P2Y12 is a protein that is expressed mainly but not solely on the surface of platelets and it regulates blood clotting (Dorsam et al 2004) making its inhibitors effective antithrombotic drugs. The inhibitor binds irreversibly to ADP -receptors on the platelet's surface resulting in inhibition for the duration of said platelet's lifespan (7-10 days) (Hashemzadeh et al 2009). Several P2Y12 -inhibitors (or ADP -receptor inhibitors), most prominently clopidogrel, ticagrelor, cangrelor and prasugrel, are available for clinical use. Inevitably effectiveness in antithrombosis and secondary prevention (Tang et al 2014) results in an increase in bleeding events; up 5.5% and 5.6% for clopidogrel and prasugrel respectively at 1 year (Brener et al 2014). A recent meta-analysis found similar major bleeding rates after PCI for novel P2Y12 –inhibitors (prasugrel, ticagrelor, cangrelor) and clopidogrel (Tang et al 2014). Bleeding rates after CABG in patients treated with thienopyridines are high i.e. in the 10-15% range and up to 41% (Hansson et al 2014, Smith et al, Tang et al 2014). When comparing different

P2Y12 –inhibitors the rates of postoperative bleeding events, however, are similar for ticagrelor and clopidogrel (Hansson et al 2014) and prasugrel and clopidogrel (Smith et al 2012) and similar for the intravenous inhibitor cangrelor and placebo (Angiolillo et al 2012).

2.2.3.1 Acetylsalicylic acid (ASA)

Acetylsalicylic acid or ASA is drug first synthesized by German chemist Felix Hoffmann in 1897 (Sneader 2000) and was long widely used mainly for its analgesic potential mediated by cyclo-oxygenase-2 (COX-2) inhibition. It also has an antiplatelet function mediated by inhibition of cyclo-oxygenase-1 (COX-1) which prevents enzymatic formation of thromboxane which in turn normally binds platelets together for clot formation and is a vasoconstrictor (Nagelschmitz et al 2014). These effects have contributed to the wide adoption of ASA as a gold standard in primary and secondary prevention of cardiovascular events (Berger et al 2006, Patrono et al 2004) although the evidence in secondary is more robust and the antithrombotic benefit outweighs the bleeding risk at conventional doses (Berger et al 2012). ASA after CABG has also been proven beneficial in preventing death and ischemic events (Antithrombotic Trialists' Collaboration 2002). Bleeding rates for ASA after treatment of ACS are significant; up to 4.8% at 12 months after stenting and up to 10.7% after medical treatment (Berger et al 2012). ASA is also a well described predictor of postoperative bleeding after CABG (Sun et al 2008), but data on bleeding after CABG in the long term is lacking.

2.2.4 Stroke

Aside from death, cerebrovascular adverse outcomes are the most dreaded complications after coronary procedures. The etiology of early postoperative stroke is thought to be related to aortic manipulation and subsequent atheromatous and other embolization, although specifically after PCI some of the strokes are rather hemorrhagic than thromboembolic in nature (Dukkipati et al 2004, Guptill et al 2013, Korn-Lubetzki et al 2013, Taggart et al 2001b). Late strokes on the other hand are more related to postoperative comorbidities such as old age, chronic obstructive pulmonary disease (COPD) and carotid artery disease (Schachner et al 2005) Large studies in the recent decades that have compared outcomes after PCI and CABG have also reported on stroke rates following both procedures. Of the recent studies, SYNTAX and a study from California described a 2-4 -fold risk of stroke both in the early postoperative (30 days) and late periods after CABG compared to PCI (Mohr et al 2013, Rudersdorf et al 2013), while ARTS and BARI described similar stroke rates (BARI investigators 1996, Unger et al 2003). A recent meta-analysis aimed at elucidating the issue of stroke after revascularization concluded that 30-day stroke rates were significantly lower with PCI (odds ratio 0.39), but there is still a paucity of studies on comparative late stroke rates (Palmerini et al 2013).

2.2.5 Repeat revascularization and myocardial infarction

Generally the most consistent differences seen between PCI and CABG in the long run are, firstly, the larger need for subsequent revascularization after percutaneous interventions and secondly, a higher rate of acute myocardial infarction (AMI) after PCI (Mohr et al 2013, Rudersdorf et al 2013). Partly the higher rates of repeat revascularization and AMI after PCI are explained by the incidence of instent restenosis and stent thrombosis. On the other hand the higher rate of reintervention and infarction might also be explained by the higher rate of incomplete revascularization with PCI seen in many studies with significant lesions developing in the untreated vessels (Farooq et al 2013a, Gao et al 2013, Ong et al 2006). In recent decades it has been shown that the use of drug eluting stents has reduced the rate of repeat revascularization due to a reduction in instent restenosis compared to bare metal stents (Kastrati et al 2007, Valgimigli et al 2014) and that the need for reintervention is a driver of adverse outcome. Disappointingly studies have failed to show a reduction in hard endpoints such as death and major adverse cardiac events (MACE) with the use of DES (Kastrati et al 2007).

2.2.6 Health-related quality of life after cardiac interventions

Contemporary results for CABG and PCI are excellent and constant efforts are underway to improve outcomes as measured by so-called hard endpoints such as those described in previous paragraphs. Consequently there has been an increased focus on health related quality of life (HRQOL) in the last 10 to 15 years. HRQOL, as generally agreed upon, is defined as the functional effect of a medical state and/or its treatment on the patient and is thus a subjective and multifaceted measure including both function in daily life and occupation, psychosocial well-being and somatic sensations (Cella 1995, Guyatt et al 1993). The World Health Organization defined HRQOL in 1997 as an "individuals perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". Interest in HRQOL in addition to concern about the quality of life of patients *per se* is also partly explained by the many aspects of HRQOL that are indicators of functional status. Poor functional status in turn translates into an increased need for supportive measures or supported living which again is linked to rising expenditures in health care (Maciejewski et al 2009, Perrin et al 2011).

A plethora of HRQOL outcome measures have been used in cardiovascular diseases (Swenson et al 2000), one of the widely used in Europe being the EuroQOL-5D or EQ-5D -questionnaire (available from the official internet site www.euroqol.org). The EQ-5D is attractive because it is simple and short, making it easy to administer and it has been validated in cardiovascular disease (Ellis et al 2005). The EQ-5D consists of two sections. The first section measures five core domains: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain consists of three levels: no problems (0), some problems (1) and severe problems (2). The second section of the

European Quality of life is a vertical visual analogue scale (VAS) ranging from 0 to 100, with 0 representing the worst and 100 the best imaginable health state.

Although cardiac surgical operations are major operations and entail loss of function and a slump in HRQOL in the early postoperative period, the HRQOL results in the long term after cardiac surgery are very good (Cohen et al 2011, Järvinen et al 2013). Even the very elderly, i.e. octogenarians and nonagenarians, have an improved quality of life after cardiac surgery (Baig et al 2013, Caceres et al 2013, Deutsch et al 2013). A recent systematic review (Jokinen et al 2010) on HRQOL after CABG reviewed 21 randomized controlled trials comparing HRQOL after off-pump and on-pump CABG; all the studies demonstrated an improvement in scores after CABG but neither of the approaches proved superior. Interestingly, the gain in quality of life appears driven by relief of angina and improved function. Although comparative studies specifically on HRQOL after CABG and PCI are scarce, it appears that they confer similar results after 6 to 12 months after the initial slump for CABG (Cohen et al 2011, Loponen et al 2009 and Rittger et al 2011) thus implying that cardiac interventions not only affect the length of life but also its quality.

2.2.7 Other risk factors for adverse postprocedural outcomes

Cardiovascular risk factors in general are numerous and well described; age, smoking, excessive alcohol consumption, obesity, hypercholesterolaemia, diabetes, peripheral arterial disease (PAD), chronic kidney disease, chronic lung disease and hypertension being among the most important (Batsis et al 2010, DeFilippis et al 2011, Go et al 2004, Kannel et al 1961, Kaplan 1989, Lopes et al 2006, Sin et al 2005 and Yusuf et al 2004). Most of these are also significant predictors of early adverse outcomes after invasive treatment (Acharjee et al 2013, Biondi-Zoccai et al 2012, Brener et al 2004, Campo et al 2013, Nashef et al 2012, Shahian et al 2009). In addition to the aforementioned general risk factors for cardiovascular events, several factors pertinent to the urgency and preoperative presentation of patients referred for revascularization affect outcome, for example: urgency (Nashef et al 2012, Romagnoli et al 2009, Shahian et al 2009), ventricular function as measured by ejection fraction (Biondi-Zoccai et al 2012, Brener et al 2004, Mancini et al 2014, Nashef et al 2012, Shahian et al 2009) and indicators of critical preprocedural status (Nashef et al 2012, Shahian et al 2009)

2.2.8 Risk scores in cardiac surgery

Cardiac surgeons have long been at the forefront of systematic procedural data collection and reporting of results; the Society of Thoracic Surgeons (STS) Database since 1990 (Grover etal 1996), the New York State cardiac surgery registry since 1990 (Hannan et al 2012) and the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons Congenital Heart Surgery Database originating from the European database from 1992 (Jacobs et al 2005) among the most prominent examples of registries. Based on the large body of of preoperative and outcome data obtained from these and other registries several validated risk scores i.e. risk stratification algorithms have been devised to encompass several separate cardiovascular and operative risk factors into one predicted risk. Debatably, the most frequently used risk algorithm for cardiac surgery in Finland is the EuroSCORE II (Nashef et al 2012). EuroSCORE II predicts operative (30 day) mortality after cardiac surgery with very good accuracy based on 18 variables (preoperative comorbidities, functional status, urgency and stability or lability of preoperative state as well as type and extent of intervention) and it has been validated in a Finnish CABG population (Biancari et al 2012). Other risk scores are more frequently used in the United States, most notably the STS risk prediction model (Shahian et al 2009). The STS risk prediction model differs from EuroSCORE II in that it also provides predictions for non-fatal postoperative complications but tends to give a higher estimate of mortality (Kunt et al 2013). Less frequently used risk prediction models are for example the Parsonnet score (Parsonnet et al 1989) and the Cleveland Clinic risk model (Higgins et al 1992).

EuroSCORE II, although intended for the prediction of postoperative outcome in cardiac surgery, might be useful for risk prediction after percutaneous interventions as well (Zhao et al 2013). Cardiologists, however, prefer the ACEF (Age, creatinine and ejection fraction) (Biondi-Zoccai et al 2012) and SYNTAX (Capodanno et al 2011) scores for risk prediction after PCI.

3. AIMS OF THE STUDY

The purpose of this study was to investigate the prognostic effect of patient-related risk factors, perioperative management, choice of coronary revascularization and their interplay as well as to identify predictors of late morbidity and mortality.

The specific questions this study addressed were:

1. Does the administering of blood products have an impact on the incidence of postoperative stroke after coronary artery bypass grafting and is the effect dose-dependent?

2. What is the mid-term survival in octogenarians after coronary revascularization and does either PCI or CABG offer a superior outcome?

3. What is the mid-term outcome of patients on oral anticoagulation for atrial fibrillation treated with PCI or CABG and do thromboembolic and bleeding issues play a significant role?

4. Does CABG affect health-related quality of life (HRQoL) measured by the EuroQOL-5D (EQ-5D) outcome measure at 6 months compared to baseline values and do the scores and changes correlate with clinical endpoints?

4. MATERIALS AND METHODS

4.1 Patient populations

The present study included patients treated invasively for CAD with PCI and stenting or isolated CABG between January 2001 and December 2011 at four Finnish Hospitals: Oulu University Hospital, Satakunta Central Hospital, Turku University Hospital and Vaasa Central Hospital. Indications for treatment were stable angina pectoris or acute coronary syndrome along with significant 1-, 2- or 3-vessel disease on coronary angiograms. 1-, 2- and 3-vessel diseases are defined in all substudies as stenosis of ≥70% diameter in an epicardial location in the main vessels or their significant tributaries (right coronary artery, left circumflex artery and/or left anterior descending artery). Left main stenosis was defined as ≥50% stenosis of the left mainstem coronary artery.

Study I included 2226 patients who underwent isolated CABG at Oulu and Turku University Hospitals and Vaasa Central Hospital between January 2008 and December 2010 and for whom complete data on preoperative blood product use (platelets, red blood cells and solvent/detergent treated plasma) was available.

Study II consisted of 274 consecutive octogenarians (≥80 of age) who underwent isolated CABG at Oulu and Turku University Hospitals between January 2001 and January 2011 as well as 393 octogenarians who underwent PCI at Turku University Hospital between January 2002 and January 2011. The starting date for PCI data collection differed from that for CABG due to the fact that records for PCI and angiographies in general were not collected prior to 2002.

The third study population comprised of 121 consecutive CABG patients treated at Oulu and Turku University Hospitals between January 2004 and December 2010 and 301 PCI patients from Oulu and Turku University Hospitals and Vaasa Central Hospital who were on oral anticoagulation with warfarin for atrial fibrillation preprocedurally.

Study IV included all 699 patients who underwent isolated CABG at Turku University Hospital during the years 2008 to 2010, 404 of whom filled out the EQ-5D -questionnaire both at baseline and 6 months (59.2% response rate) and were further analyzed.

All studies were approved by institutional review boards of either Oulu or Turku University Hospital districts.

4.2 Description of procedures

CABG procedures were performed from median sternotomy on cardiopulmonary bypass or as off-pump surgery based on anatomical consideration (e.g. in cases of calcified ascending aorta) and the individual surgeon's preference and experience. The left anterior descending artery was preferably grafted with the LIMA when feasible and secondary grafts were arterial or venous based on availability and the operating surgeons choice. Systemic heparinization was administered to achieve an activated clotting time over 400 seconds before institution of bypass or grafting in case of off-pump surgery. Protamine sulphate (1.5-3.0 mg/kg) was administered at the end of surgery to neutralize heparin. Tranexamic acid was used at the anesthesiologists discretion. Blood products (Octaplas®, red blood cells and platelets) were administered based on bleeding, international normalized ratio (INR) and whole blood counts. Clopidogrel and aspirin were discontinued 5 to 7 days prior to surgery unless surgical intervention could not be postponed. Warfarin was mainly discontinued for 2 days prior to CABG without heparin bridging. Enoxaparin 40-80 mg subcutaneously was started for all patients on the evening of surgery and warfarin was started on the first postoperative day when indicated. Postoperative clopidogrel at 75 mg per day was started in patients when indicated by recent coronary stenting or ASA allergy.

All PCI procedures in this data included stenting with bare metal stents or drug eluting stents based on the clinical scenario and the treating cardiologist's discretion. Radial or femoral artery access was used according to the cardiologist's preference. Uninterrupted oral anticoagulation was used for patients with an indication for warfarin. Glycoprotein IIb/IIIa inhibitors and bivalirudin were used periprocedurally at the treating physicians discretion. Preprocedural clopidogrel and ASA were managed according to local practices and the treating physician's discretion.

4.3 Study design

The study designs were retrospective cohort studies (II, III and IV) and a retrospective cross-sectional study (I). Data on baseline comorbidites and medication, periprocedural treatment, in-hospital outcomes, discharge medication and postprocedural adverse outcomes were collected from electronic patient records. Follow-up for these data were complete as patients resided within the catchment areas of Oulu and Turku University Hospitals as well as Satakunta and Vaasa Central Hospital for the treatment of the measured outcomes. Data on date and mode of death was complete and was obtained from the Finnish national registry, Statistics Finland.

Data for Study I was collected as part of a larger study assessing blood product use and bleeding complications in cardiac surgery in Western Finland. To identify the use of blood products as predictors of stroke, the amounts were divided into classes: 0, 1-2 or >2 units of red blood cells (RBC), 0, 1-8 or >8 units of platelets and 0, 1-4 or >4 units of Octaplas®. The sum of these products was used as an estimate of blood product consumption and indicator of patients who received large amounts of products (with the assumption that those receiving the highest classes were at the highest risk of stroke). Data was collected up to discharge or in-hospital death.

Data-collection periods were January 2001 to January 2011 for Study II (no data on PCI prior to 2002 due to lack of electronic records). Mean follow-up was 3.6 ± 2.6 years.

Baseline data on patients for Study III was originally collected for the AFCAS –study (www.clinicaltrials.gov/ ct2/show/NCT00596570); from 2000 to 2010 for PCI patients (Oulu and Turku University Hospitals and Satakunta Central Hospital) and from 2004 to 2010 for CABG patients (Oulu and Turku University Hospitals). Patients who had other indications for warfarin in addition to AF (e.g. heart valve prostheses, thromboembolic complications etc.) were excluded and data was complemented with information on late adverse events and data on mode and date of death up to last follow-up in June 2011. Mean follow-up was 2.9±1.6 years.

Table 1. Adverse events 6 months or later after isolated CABG (404 patients) and time to event.

MACCE type	Number of events	Median time to event (days)	Range (days)
Stroke/TIA	17	779	213-1602
Myocardial infarction	11	558	536-772
Cardiac death	8	840	475-1128

The patient population for study IV was the same as for study I from Turku University Hospital complemented with data on late adverse events and date and mode of death as well as HRQOL scores at baseline and 6 months postoperatively. Last follow-up was in June 2012. HRQOL scores were measured with the EQ-5D –questionnaire for all patients as part of routine quality control at the intensive care unit of Turku University Hospital. Patients undergoing elective or urgent surgery filled out the questionnaire on the day prior to surgery and patients undergoing emergency surgery filled out the questionnaire as soon as they were able. Patients were asked to describe the quality of life of the last 2 weeks preceding surgery. All surviving patients were sent the second questionnaire by mail at 6 months postoperatively and in case of non-responders a maximum of two repeat questionnaires were sent. The obtained population was divided into two study groups: patients who did not suffer subsequent adverse events (No MACCE -group) and patients who suffered adverse events after completion of the second questionnaire at 6 months (MACCE –group). Adverse events and time to their occurrence are described in table 1. Mean follow-up was 38.6±10.5 months from index operation.

4.4 Outcome endpoints

Main outcome endpoints were all-cause mortality, occurrence of stroke, repeat revascularization, acute myocardial infarction, major bleeding, health related quality of life and major adverse cardiac and cerebrovascular events (MACCE) at follow-up.

Predictors of adverse events were also assessed as descriptors of outcome.

Stroke was defined as a new neurological deficit that lasted over 24 hours and was accompanied by a radiographic finding on computed tomography or magnetic resonance imaging. In cases where no radiographic confirmation was seen or available, stroke was based on clinical findings on examination by a neurologist.

Acute myocardial infarction was defined as new onset symptoms suggestive of myocardial infarction accompanied by ST-segment elevations or cardiac biomarker level changes in accordance with the 3rd edition of the Universal Definition of Myocardial Infarction (Thygesen et al 2012).

Repeat revascularization was defined as any new non-staged PCI (including balloon angioplasty) or CABG procedure performed after the index procedure.

Major bleeding was defined as cardiac tamponade, intracranial bleeding, any fatal bleeding or any bleeding requiring operative intervention.

MACCE was defined as a composite of death, myocardial infarction, stroke, repeat revascularization and major bleeding in study III and a composite of death, myocardial infarction and stroke in Study IV.

Health-related quality of life and changes thereof were measured with the EuroQOL-5D instrument.

4.5 Statistical analyses

All statistical analyses were performed with SPSS v. 17-20 statistical software (IBM SPSS Inc., Chicago, Ill., USA).

A p-value of <0.05 was considered statistically significant. Continuous variables are reported in mean ± standard deviation. HR indicates hazard ratio and CI indicates confidence interval

In study I Pearson’s chi-square test, Fisher’s exact test and Mann-Whitney’s test were used for univariate analysis. Correlations between continuous variables were assessed by Spearman’s test. Multivariate analysis employed Cox’s regression method with backward selection and including only variables of statistical significance on univariate analysis. Predetermined cutoff values for amounts of transfused blood products were confirmed on Classification and regression tree (CART) analysis. A propensity score was calculated to control for all known patients’ factors that might be related to the decision to administer blood products. The propensity score was used to adjust when determining predictors of stroke.

Study II employed Fisher’s exact test, the Mann-Whitney *U* test, and the Kaplan-Meier test for univariate analysis. The Log-rank (Mantel-Cox) method was used to evaluate between groups differences on Kaplan-Meier –analysis. Logistic and Cox regression analyses with backward selection by including variables with $p < 0.05$ on univariate analysis were used for multivariate analysis. To adjust for differences in treatment method a propensity score was calculated and this was used for adjustment.

Baseline differences and differences in EQ-5D –scores in study III were evaluated with independent samples T-test (2-tailed significance) and Pearson's chi-square test. Multivariate analysis was performed using the Cox proportional hazards model with backward selection including age, gender, history of stroke, preoperative AF, left ventricular ejection fraction, length of in-hospital stay, postoperative resternotomy, EQ-5D-scores and postoperative stroke.

In study IV Chi-square test, Fisher exact test, Mann-Whitney test and Kaplan-Meier test used for univariate analysis. The Log-rank (Mantel-Cox) method was used to evaluate between groups differences on Kaplan-Meier –analysis. Multivariate analysis was performed with the Cox regression method by including variables of clinical relevance. A propensity score was calculated to adjust for between groups' differences.

CART (Classification and regression tree) analysis

In study I classification and regression tree (CART) analysis was used for regression analysis to identify predictors of immediate postoperative adverse events. Validation of the classification tree procedure was assessed by cross-validation through 25 folds. The minimum number of patients for the parent node was set at 30 and the minimum for the child node was 1. The maximum classification tree depth was 5. minimum change in improvement was set at 0.0001. Receiver operating characteristic (ROC) curve analysis was used to estimate the area under the curve of probabilities values estimated by the CART analysis model.

Propensity score analysis

Propensity scores are calculated to overcome selection bias in observational data in datasets where the variables that affect the measured outcome are predictive of assignment to a treatment modality specifically when said treatment is the main predictor studied. It enables matching with lesser loss of a large number of cases. Propensity score matching (PSM) is useful when few cases between the studied treatment groups are comparable and obtaining comparable groups is not feasible or possible. The obtained score can be used to match cases from studied groups that have a similar probability of being assigned to either treatment or it can be used as a covariate.

The propensity scores for studies I to III were calculated by logistic regression analysis with backward selection by including clinical variables with $p < 0.05$ on univariate analysis for studies I and III and $p < 0.20$ on univariate analysis for study II. The score was used for one to one matching and for overall risk adjustment in I and II. One to one propensity score matching between the study groups was done with a caliber width of 0.2 of the standard deviation of the logit estimated according to Austin (Austin 2011). ROC curve was analyzed to assess the area under the curve for the obtained propensity score. Because of the limited size of the study population in study III, the estimated propensity score was employed only for risk adjusted analysis i.e. as a covariate in any regression model.

5. RESULTS

5.1 Baseline data

Clinically and statistically significant baseline differences between groups are presented in tables 2 (Study II), 3 (Study III), 4 (Study IV) and table 6 (Study I).

Table 2. Baseline variables for patients >80 years undergoing PCI or CABG.

	Overall series			Propensity score –matched pairs		
Group	**CABG n=273**	**PCI n=392**	**p-value**	**CABG n=130**	**PCI n=130**	**p-value**
Age (years)	82.0 ± 1.7	83.3 ± 2.5	<0.0001	82.5 ± 2.0	82.6 ± 2.1	0.808
Females	107 (39%)	193 (49%)	0.010	48 (37%)	59 (45%)	0.166
Prior cardiac surgery	4 (2%)	31 (8%)	<0.0001	4 (3%)	3 (2%)	1.000
Diseased vessels			<0.0001			0.488
1	5 (2%)	83 (21%)		5 (4%)	3 (2%)	
2	30 (11%)	170 (43%)		27 (21%)	34 (26%)	
3	238 (87%)	139 (36%)		98 (75%)	93 (72%)	
AMI <90d	154 (56%)	303 (77%)	<0.0001	91 (70%)	84 (65%)	0.355
Emergent procedure	26 (10%)	125 (32%)	<0.0001	23 (18%)	24 (19%)	0.872

Continuous variables in mean±standard deviation. AMI = acute myocardial infarction, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention. All definitions according to the EuroSCORE –criteria (www.euroscore.org)

At baseline octogenarians undergoing PCI as compared to those undergoing CABG were significantly older, more often female, had had previous cardiac surgery or had a recent AMI and more often underwent emergent procedures. CABG patients more often had 3-vessel disease. There were no statistically significant differences in baseline variables between propensity matched octogenarian groups.

At baseline, patients on OAC for AF who underwent PCI compared to those who underwent CABG were significantly older, more often female, more often had hypertension or prior cardiac surgery and ACS. PCI patients also more often had ASA, clopidogrel, statins and β-blockers at discharge. CABG patients on the other hand more often had 2- or 3-vessel disease and left main stenosis.

Table 3. Baseline variables for patients on oral anticoagulation with warfarin undergoing PCI or CABG

	CABG group (n=121)	PCI group (n=301)	p-value
Age (years)	69.8±8.5	72.9±7.7	<0.001
Age ≥ 80 years	11 (9.1%)	58 (19.3%)	<0.001
Females	19 (15.7%)	79 (26.2%)	0.020
Hypertension	83 (68.6%)	236 (78.4%)	0.034
Stroke/transient ischemic attack	19 (15.7%)	65 (21.6%)	0.170
Prior cardiac surgery	2 (1.7%)	48 (15.9%)	<0.001
Acute coronary syndrome	26 (21.5%)	162 (53.8%)	<0.001
Two or three-vessel disease	115 (95.0%)	181 (60.2%)	<0.001
Left main stenosis	39 (32.2%)	21 (7.0%)	<0.001
LVEF <30%	6 (5.0%)	14 (4.7%)	1.000
Preoperative INR	1.9±0.6	2.3±0.6	0.067
$CHADS_2$ -score	2.0±1.2	2.1±1.2	0.613
Aspirin at discharge	59 (49.6%)	275 (91.4%)	<0.001
Clopidogrel at discharge	8 (6.8%)	291 (96.7%)	<0.001
Statin at discharge	88 (73.9%)	262 (89.1%)	<0.001
β-blockers at discharge	110 (93.2%)	257 (87.4%)	0.088

Continuous variables in mean±standard deviation. AMI = acute myocardial infarction, CABG=coronary artery bypass grafting, $CHADS_2$=Congestive heart failure, Hypertension, Age≥75 years, Diabetes, Prior Stroke or TIA or Thromboembolism (Gage et al 2001), LVEF=left ventricular ejection fraction, INR = international normalized ratio, PCI=percutaneous coronary intervention

At baseline patients in study IV who suffered late MACCE as compared to those who didn't more often had a LVEF<30% and more often had suffered in-hospital postoperative strokes.

Table 4. Baseline variables for patients with and without late (>6 months postoperatively) MACCE after isolated CABG.

Variable	No MACCE–group(n=369)	MACCE –group(n=35)	p-value
Age (years)	66.1 ± 8.1	67.6 ± 9.5	0.35
Females	86 (23.3%)	8 (22.9%)	0.95
Recent AMI <90d	59 (16.0%)	6 (17.1%)	0.86
LVEF <30%	15 (4.1%)	5 (14.3%)	0.008
Urgent/emergent CABG	144 (39.0%)	14 (40.0%)	0.91
In-hospital stay (days)	7.6 ± 3.5	8.8 ± 7.0	0.08
In-hospital postoperative stroke	2 (0.5%)	8 (22.9%)	0.001

Continuous variables in mean±standard deviation. AMI=acute myocardial infarction, CABG=coronary artery bypass grafting, LVEF=left ventricular ejection fraction, MACCE=major adverse cardiac and cerebrovascular event

5.2 Survival

In-hospital mortality after CABG was 2.2% (Study I). Mortality at 30 days for CABG vs PCI was 8.8% vs 7.4% for octogenarians and 3.3% vs 2.3% for patients on OAC. Actuarial survival is shown in figures 1-3. Predictors of survival for patients >80 years old are shown in table 5.

Table 5. Predictors of mortality in octogenarians after PCI or CABG.

Variable	Cox proportional hazard (HR, 95% CI)
Age	1.118, 1.056–1.183
Serum creatinine	1.006, 1.004–1.008
Pulmonary disease	1.941, 1.344–2.804
Diabetes	1.627, 1.193–2.218
Recent AMI <90d	1.606, 1.163–2.217
Neurologic dysfunction	2.575, 1.254–5.289
Peripheral arterial disease	1.557, 1.045–2.319
Emergent procedure	1.644, 1.202–2.249

AMI=acute myocardial infarction, CABG=coronary artery bypass grafting, CI=confidence interval, HR=hazard ratio, PCI=percutaneous coronary intervention. Criteria as in Euroscore.

In patients on OAC for AF after adjusting for age, gender, previous cardiac surgery, recent AMI, ACS, left main stenosis and multivessel disease, patients treated with PCI had a higher predicted risk of mortality compared to CABG patients (HR 2.035, 95% confidence interval 1.049-3.949) and also after adjusting for propensity score (HR 2.166, 95% confidence interval 1.155-4.060).

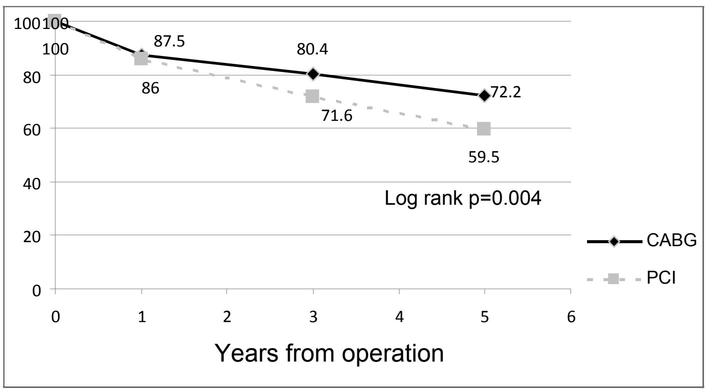

Figure 1. Unadjusted survival (%) of octogenarians after PCI and CABG.

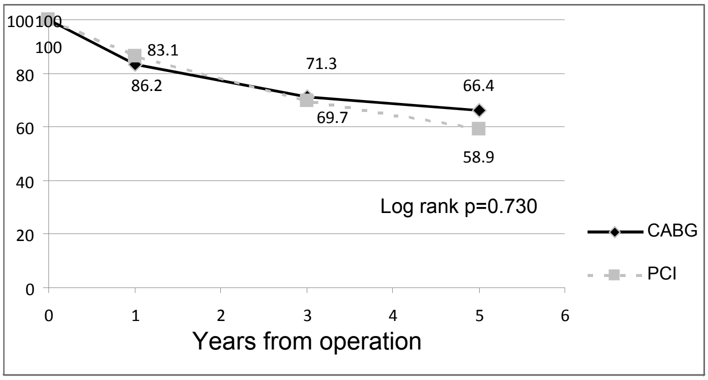

Figure 2. Propensity score adjusted survival (%) of octogenarians after PCI and CABG.

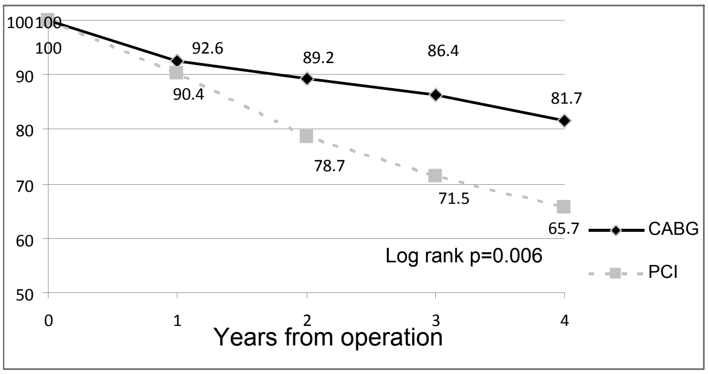

Figure 3. Survival (%) for patients on OAC for atrial fibrillation after CABG and PCI.

5.3 Stroke

Predictors of stroke are shown in tables 6 (Study I) and 7 (Study IV).Treatment group (PCI or CABG) did not predict stroke on Cox regression in patients on OAC for AF (Study III) with or without adjustment for propensity score.

Actuarial freedom from stroke in Study III is presented in figure 4. Frequency of stroke according to different amounts of postoperative blood product administration are demonstrated in figures 5 and 6 and results of the CART –analysis in figure 7.

Table 6. Predictors of postoperative stroke (n of strokes = 53, 2.4%) after isolated coronary artery bypass grafting (n=2226).

Variable	Value	Univariate analysis (p-value)	Multivariate analysis (OR, 95% CI)
Age (years)	67.1±9.2	0.047	
Creatinine (µmol/L)	90±52	<0.0001	1.003, 1.000-1.006
Atrial fibrillation (preoperative)	187 (8.4%)	0.011	
Peripheral arterial disease†	201 (9.0%)	0.011	2.409, 1.149-5.052
Preoperative clopidogrel	613 (27.5%)	0.030	
Left ventricular ejection fraction		0.037	
>50%	1651(74.2%)		
30-50%	449(20.2%)		
<30%	100 (4.5%)		
Unstable angina†	329 (14.8%)	0.010	
Low cardiac output sdr, postoperative†	324 (14.6%)	0.001	
RBC transfusion	1134(50.9%)	0.005	
RBC units transfused	2.0±3.1	<0.0001	1.121, 1.065-1.180
Octaplas® transfusion	486 (21.8%)	<0.0001	
Octaplas® units transfused	0.8±2.0	<0.0001	
Platelet transfusion	458 (20.6%)	<0.0001	
Platelet units transfused	1.8±4.9	<0.0001	
De novo dialysis	41 (1.8%)	<0.0001	
Atrial fibrillation (postoperative)	799 (35.9%)	0.043	

Continuous variables as mean±standard deviation, CI = confidence interval, OR = odds ratio, RBC = red blood cell, †as in EuroSCORE

Table 7. Predictors of late (> 6 months) postoperative stroke after CABG.

Variable	Cox proportional hazards model (HR, 95% CI)
In-hospital stay (per day)	1.271, 1.123-1.438
Postoperative in-hospital stroke	24.159, 5.946-98.1
Deteriorating EQ-5D Usual activities –score (per unit)	2.731, 1.219-6.119

CI = confidence interval , EQ-5D = EuroQOL-5D quality of life questionnaire, HR = hazard ratio

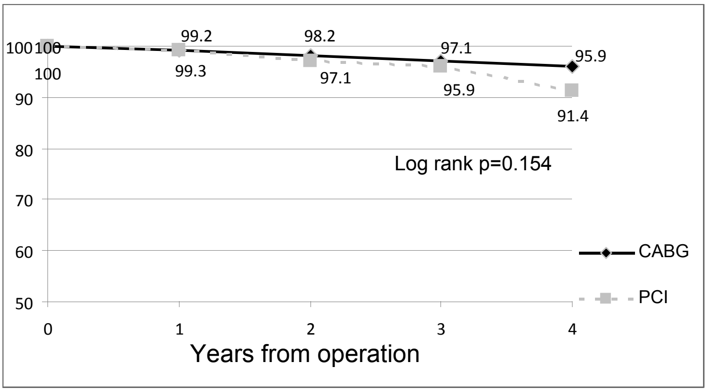

Figure 4. Freedom from stroke (%) for patients on OAC for atrial fibrillation.

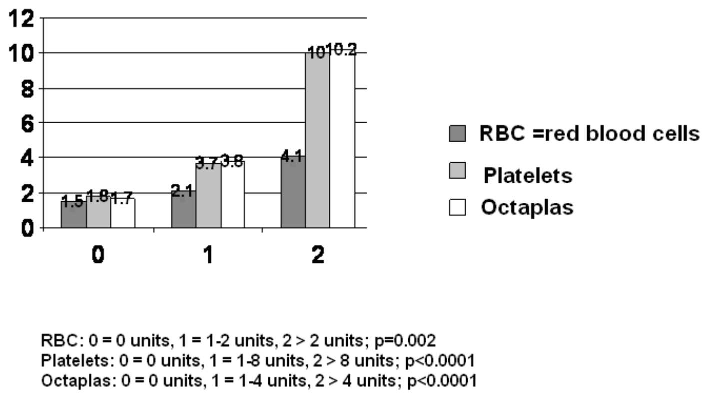

Figure 5. Frequency of stroke (%) after coronary artery bypass grafting according to amount of transfused blood product.

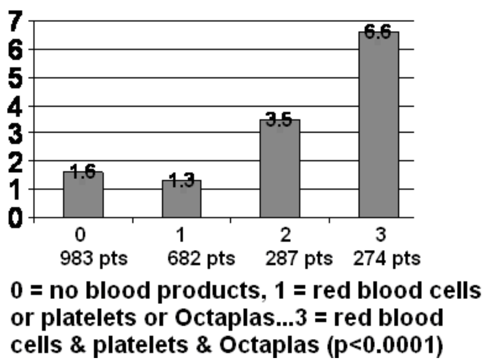

Figure 6. Postoperative stroke rates (%) after coronary artery bypass grafting according to the sum of any type of transfusion.

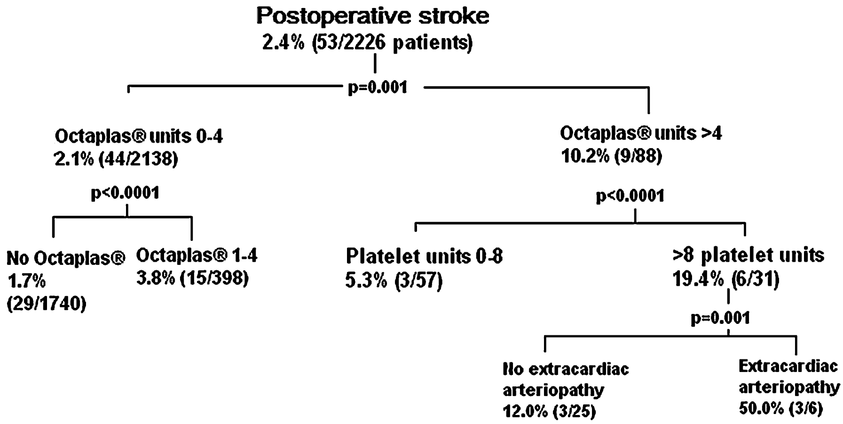

Figure 7. CART -analysis of postoperative stroke after CABG.

5.4 Bleeding

Rates of in-hospital bleeding events are summarized in table 8.

Table 8. In-hospital bleeding events after coronary revascularization.

	CABG (study I) n = 2226	CABG (OAC for AF) n = 121	PCI (OAC for AF) n = 301	CABG (study IV) n = 404
Cardiac tamponade, operated	6.2%	2.5%	0.3%	4.8%
Access site bleeding, operated	-	-	1.3%	-
Intracranial bleeding	0%	0%	1.0%	0%
Gastrointestinal bleeding	0%	0%	0.7%	0%
Airway bleeding	0%	0%	0.3%	0%
RBC transfusion	50.9%	-	-	-
Platelet tranfusion	20.6%	-	-	-
Octaplas® transfusion	21.8%	-	-	-

AF = atrial fibrillation, CABG = coronary artery bypass grafting, OAC = oral anticoagulation (with warfarin), PCI = percutaneous coronary intervention, RBC = red blood cell

Post-discharge freedom from major bleeding events after PCI and CABG in patients on OAC for AF is demonstrated in figure 8. For patients on OAC for AF, treatment method was not a predictor of bleeding on logistic regression.

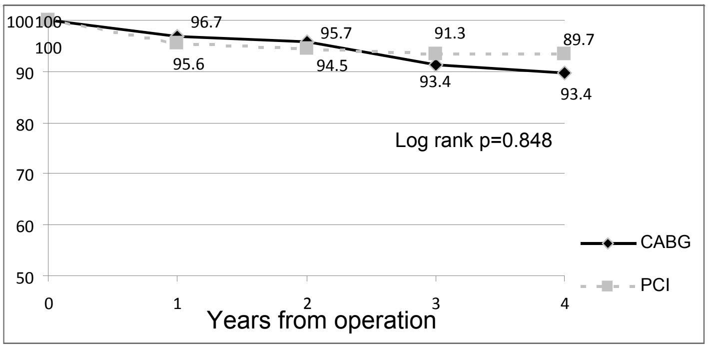

Figure 8. Freedom from major bleeding (%) for patients on OAC for atrial fibrillation after CABG and PCI.

5.5 Acute myocardial infarction

Patients who underwent isolated CABG in study IV experienced 11 late (> 6 months postoperatively) myocardial infarctions resulting in 0.004/ person year.

Freedom from myocardial infarction after PCI and CABG in patients on OAC for AF is demonstrated in figure 9.

In patients on OAC for AF being assigned to PCI compared to CABG independently predicted myocardial infarction on logistic regression (HR 3.92, 95%CI 1.01-15.2). After adjustment for propensity score PCI was still a predictor of AMI (p=0.017, HR 3.161, 95%CI 1.227-8.144).

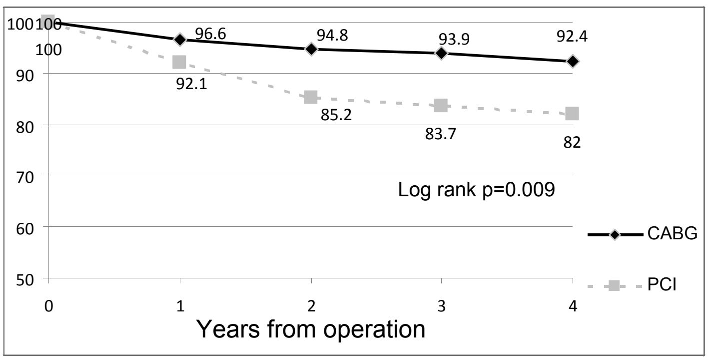

Figure 9. Freedom from myocardial infarction (%) for patients on OAC for atrial fibrillation after CABG and PCI.

5.6 Repeat revascularization

In study IV, there were 15 PCI procedures performed on the patients during follow-up resulting in 0.01/ person year.

Freedom from repeat revascularization after PCI and CABG in patients on OAC for AF is demonstrated in figure 10.

In patients on OAC for AF PCI was an independent predictor of repeat revascularization on logistic regression after adjustment for propensity score (p=0.002, HR 11.302, 95%CI 2.430-52.562).

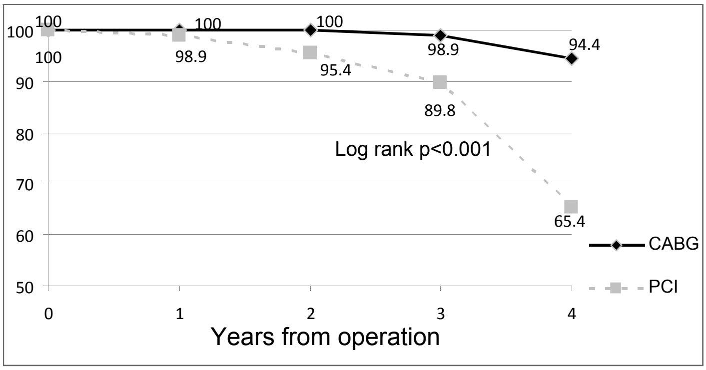

Figure 10. Freedom from repeat revascularization (%) for patients on OAC for atrial fibrillation after CABG and PCI.

5.7 Major adverse cardiac/cerebrovascular events (MACCE)

There were 36 occurences of MACCE in 35 patients in Study IV during follow-up resulting in 0.03/ person year. Freedom from MACCE after PCI and CABG in patients on OAC for AF is demonstrated in figure 11.

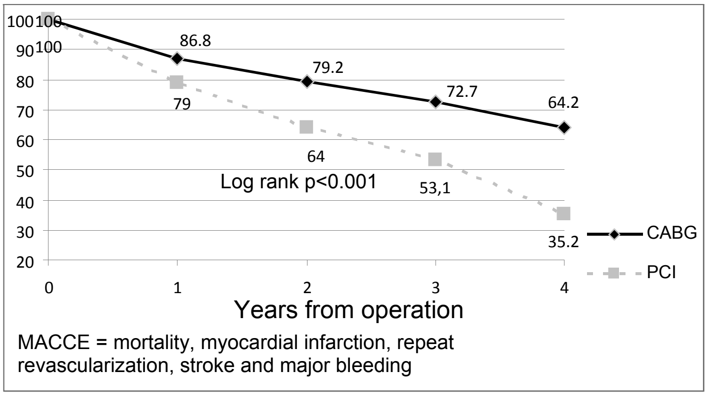

Figure 11. Freedom from MACCE (%) for patients on OAC for atrial fibrillation after CABG and PCI.

Predictors of MACCE after CABG are shown in table 9.

PCI was and independent predictor of MACCE in patients on OAC for AF on logistic regression (HR 4.9, 95%CI 1.63-14.7). After adjustment for propensity score PCI remained a predictor of MACCE (HR 2.347, 95%CI 1.408-3.914).

Table 9. Predictors of late (> 6 months) MACCE after CABG.

Variable	Cox proportional hazards model (HR, 95% CI)
History of stroke	7.287, 1.658-32.018
In-hospital stay (days)	1.076, 1.015-1.141
Lower EQ-5D VAS at 6 months (per unit)	1.040, 1.011-1.068
Negative changes on VAS between 0 and 6 months (per unit)	1.047, 1.007-1.089
Negative change in EQ-5D Usual activities -score from 0 to 6 months (per unit)	2.589, 1.278-5.245

CI = confidence interval , EQ-5D = EuroQOL-5D quality of life questionnaire, HR = hazard ratio, MACCE = major adverse cardiac and cerebrovascular event (death, stroke, myocardial infarction), VAS = visual analogue scale

5.8 Health related quality of life (HRQOL)

EQ-5D –scores are summarized in table 10. Statistically significant differences in changes for EQ-5D –scores between MACCE –patients and No MACCE –patients are visualized in figures 12 and 13 and changes in VAS –scores in figure 14. MACCE –patients scored worse at 6 months on VAS and declined on the caring for self – and usual activities subscales between baseline and 6 months.

Table 10. EuroQOL-5D scores at baseline and 6 months after isolated coronary artery bypass grafting.

	No MACCE	MACCE	p-value
VAS, 0 months	65.9 ± 21.2	67.1 ± 14.9	0.77
Mobility, 0 months	1.51 ± 0.62	1.49 ± 0.66	0.86
Caring for self, 0 months	1.13 ± 0.40	1.12 ± 0.33	0.90
Usual activities, 0 months	1.19 ± 0.46	1.08 ± 0.28	0.22
Pain, 0 months	1.71 ± 0.59	1.57 ± 0.61	0.18
Anxiety/depression, 0 months	1.29 ± 0.51	1.11 ± 0.32	0.005
VAS, 6 months	77.2 ± 16.5	68.2 ± 20.2	0.004
Mobility, 6 months	1.37 ± 0.50	1.43 ± 0.56	0.52
Caring for self, 6 months	1.10 ± 0.33	1.20 ± 0.47	0.10
Usual activities, 6 months	1.31 ± 0.52	1.49 ± 0.66	0.06
Pain, 6 months	1.44 ± 0.53	1.51 ± 0.51	0.45
Anxiety/depression, 6 months	1.18 ± 0.40	1.17 ± 0.38	0.94
ΔVAS	11.8 ± 24.1	3 ± 22.6	0.07
ΔMobility	−0.14 ± 0.69	−0.06 ± 0.68	0.52
ΔCaring for self	−0.05 ± 0.43	0.16 ± 0.55	0.03
ΔUsual activities	0.07 ± 0.60	0.48 ± 0.71	0.01
ΔPain	−0.27 ± 0.69	−0.06 ± 0.73	0.09
ΔAnxiety/depression	−0.11 ± 0.58	0.06 ± 0.48	0.10

MACCE = major adverse cardiac and cerebrovascular event (death, stroke, myocardial infarction), VAS = visual analogue scale (0-100). Δ = change from 0 and 6 months. Positive changes on VAS and negative changes on subscales indicate improvement. Values mean±standard deviation.

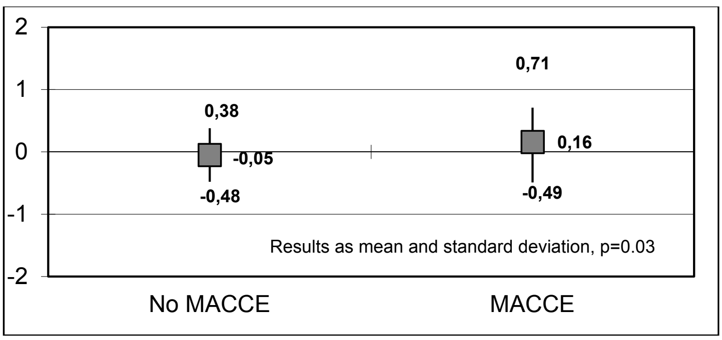

Figure 12. Change on EQ-5D caring for self -subscale scores between 0 and 6 months postoperatively after CABG for patients with and without late MACCE (death, stroke or AMI).

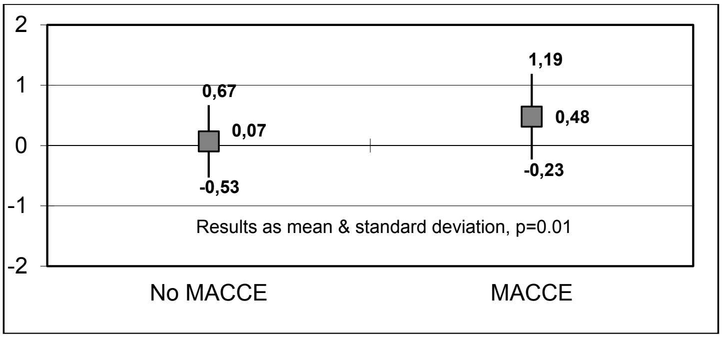

Figure 13. Change on EQ-5D usual activities -subscale scores between 0 and 6 months postoperatively after CABG for patients with and without late MACCE (death, stroke or AMI).

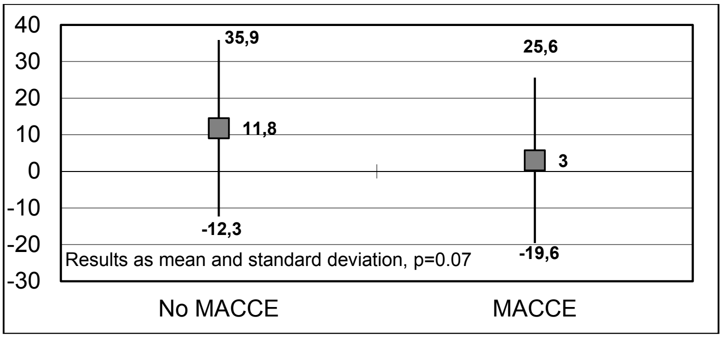

Figure 14. Change on EQ-5D visual analogue scale scores between 0 and 6 months postoperatively after CABG for patients with and without late MACCE (death, stroke or AMI).

6. DISCUSSION

6.1 Blood products and the risk of postoperative stroke

Transfusion of blood products is a frequent occurrence after cardiac surgery; in the United States, 20% of blood transfusions are given after cardiac surgery although cardiac surgery does not account for nearly that proportion of all surgical procedures. Up to 60% of cardiac operative patients receive blood transfusions (Snyder-Ramos et al 2008, Speiss et al 2002, Stover et al 1998). Although preoperative anemia is a risk factor for adverse outcome after cardiac surgery (Karkouti et al 2008, van Straten et al 2009) and thus partially explains the correlation between blood product administration and adverse events in this study, there is increasing evidence that administration of blood products is also independently linked to postoperative complications after cardiac surgery: postoperative infections (Chelemer et al 2002, Rogers et al 2009, Sharma et al 2002, Solh et al 2006), short- and long-term mortality (Engoren et al 2002, Kuduvalli et al 2005, Murphy et al 2007, van Straten et al 2010, Surgenor et al 2009), acute kidney injury (Karkouti et al 2011) and even gastrointestinal complications (Hashemzadeh et al 2012). Interestingly, a study comparing Jehovah's witnesses (who do not receive blood products at all due to religious restrictions) with a normal cardiac surgical population corroborated the link between blood transfusion and adverse outcomes (Pattakos et al 2012). Our study showed that the previously described correlation between blood product administration is dose-dependent and administration of all three types of blood products is especially detrimental. In daily practice, an ever more meticulous hemostasis and a conservative approach to transfusions might help prevent postoperative strokes.

6.2 Octogenarians and revascularization

The main finding of this study concerning revascularized octogenarians was that overall CABG conferred better survival than PCI at 5-years follow-up. Survival was at 70 % after CABG which is comparable to the 73.3% of the age-matched general population (Statistics Finland) and a previous report from Finland (Vasques et al 2013). Mortality for CABG in the present study was 8.8% which is somewhat higher than that reported by others (McKellar et al 2008, Raja et al 2013, Vasques et al 2013), but taking into account the excellent long-term results, probably reflects a confident approach in operating octogenarians in Western Finland. Additionally patient selection probably varies between studies. Results for PCI were also in line with previous reports (McKellar et al 2008, Rittger et al 2012), although these did not elaborate on long-term follow-ups.

Multivariate analysis suggested that there was no difference in outcome between octogenarians treated with PCI and CABG. This is most certainly due to a selection bias.

In other words, although baseline values do not appear very different, after adjustment they cannot account for clinically evident factors in the elderly, namely frailty and dementia. Frailty has been repeatedly shown to be a predictor of poor outcome in elderly patients (Ekerstad et al 2011, Partridge et al 2012, Sirola et al 2011,). Its usefulness in risk prediction has been alluded at (Afilalo et al 2012, Bagnall et al 2013) and it would be interesting to know how matching or stratifying the two groups for frailty would influence the results, as the presence of frailty has been demonstrated to increase mortality for cardiac surgery and transcatheter valve replacement 2 to 4 –fold (Green et al 2012, Lee et al 2010, Sundermann et al 2014). Quantifying frailty in real life, however, can be foreign to cardiovascular clinicians and overall the predictive accuracy is not self-evidently established as there is a significant amount of false positive classification with frailty assessment tools (Daniels et al 2012, Pijpers et al 2012).

It appears that careful selection and assessment of frailty bedside are needed when weighing treatment options in octogenarians.

6.3 Warfarin treatment and outcomes after coronary revascularization

The present study presents the only direct comparison of outcomes for patients with warfarin for AF who have undergone coronary revascularization. It appears that in Western Finland patients on OAC for AF are treated fairly accurately according to general recommendations on choice of revascularization based on the differences in preoperative characteristics and distribution of single-vessel and multi-vessel disease.

Within this data, the major finding was that 3-year survival and freedom from MACCE are better for patients treated with CABG even when adjusted for important clinical variables or propensity score. Mortality was relatively high during follow-up (13.6% for CABG and 28.0% for PCI at 3 years) when comparing to general CABG and PCI populations, but in line with earlier reports on patients with preoperative atrial fibrillation (Bramer et al 2010, Ngaage et al 2007, Tanaka et al 2012). This underlines the notion that patients with AF are at a high risk for mortality. This study had a small proportion of patients who underwent surgical ablation for AF during CABG. It would be interesting to know how a more aggressive approach towards ablation would affect long-term survival. Although there is currently good evidence that ablation appears effective in reducing recurrence of AF (Damiano et al 2013, Proietti et al 2014, Santangeli et al 2013) there is no direct evidence of a mortality benefit from ablation and even the effect on HRQOL is ambiguous (Neyt et al 2013). There is, however, an ongoing study comparing catheter ablation to conservative treatment which might elucidate this question (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial, ClinicalTrials.gov NCT00911508).

Our study showed similar rates of major bleeding episodes for both treatment groups during the entire follow-up. Bleeding is a complication feared by both patients and clinicians. This is reflected by a previous study showing that patients with long-term OAC with warfarin are less likely to be referred for coronary angiography and invasive treatment, primarily due to fear of bleeding (Wang et al 2008). This fear, however, appears exaggerated based already on an earlier study on CABG bleeds (Airaksinen et al 2011) and similarily, studies on PCI have reported comparable proportions of bleeding events for patients with and without OAC (Kiviniemi et al 2012, Rossini et al 2008, Rubboli et al 2013, Yoon et al 2013). The present study corroborates that bleeding events are rather infrequent during the early perioperative period and that there is no difference between PCI and CABG patients on warfarin. Serious bleeding events in this data even during 3-years follow-up were also identically frequent in groups and bleeding rates for PCI were similar to earlier reports (Enomoto et al 2013, Hansen et al 2010).

MACCE rates at 3 years were lower after CABG which is partly explained by a higher incidence of AMI and repeat revascularization after PCI, which again is in line with data on patients with no OAC as previously shown (Mohr et al 2013).

Although the data herein presented is the best comparative data available, it has several limitations. Most importantly, the data is retrospective and quite small, which makes adjusting for confounders difficult as many baseline values cannot be accounted for based on patient records. This makes the data primarily descriptive. Although no superiority can be established based on this data it can be speculated that the findings described here offer no reason to deviate from general recommendations on choice between PCI and CABG based on presence of warfarin treatment.

6.4 HRQOL and its correlation with late outcome

In the present study, lower scores on the EuroQOL-5D Visual Analogue Scale correlated with later MACCE. Worsening scores on the VAS and on the Usual activities subscale between 0 and 6 months after CABG were independent predictors of later MACCE on Cox regression analysis. Patients who did not experience later MACCE reported VAS-scores comparable to population norms. Declining function as measured by the Usual activities subscale also predicted stroke.

Non-responders (i.e. CABG patients from the same time period who did not fill out both EQ-5D –questionnaires) were more often in need of acute surgery, more often had a recent AMI and more often had a depressed ejection fraction but otherwise similar in regards to baseline variables. This could potentially bias the EQ-5D –results; acute patients often filled out the questionnaire postoperatively which gives rise to a potential for recollection bias as patients were asked to assess HRQOL within the 2 weeks preceding surgery. Consequently non-responders who underwent acute surgery might have judged their HRQOL lower than it actually was. Excluding these patients, however, most likely only dilutes the results and consequently would not alter the conclusions.

Previous studies have identified several cardiovascular risk factors that influence quality of life in CAD patients and after cardiac surgery (De Smedt et al 2013, Grothusen et al 2013, Koch et al 2004, Sjöland et al 1999); preoperative quality of life, gender, baseline comorbidities (AF, COPD, lowered EF, history of AMI or stroke, diabetes, peripheral arterial disease etc.) and postoperative complications (infection, resternotomy for bleeding, postoperative stroke, etc.). Many of these are known risk factors for mortality after CABG (Mattila et al 1990, Toumpoulis et al 2004 and 2006). Psychological factors have also been shown to affect HRQOL after CABG, but whether these are truly independent predictors or markers of HRQOL is debatable (Middel et al 2013), although Vainiola et al, in contrast, showed in their 2013 study that factors affecting mortality and HRQOL after CABG can be different. It can be speculated that quality of life might be a compound indicator of risk factor burden which is actually in concordance with the World Health Organization definition: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

Other studies have already shown that self-reported HRQOL predicts later survival in other patient populations such as patients with congestive heart failure, elderly nonsurgical patients, patients with atrial fibrillation and surgical cancer patients (Chapa et al 2013, DeAguiar et al 2013, Djärv et al 2011, Hoekstra et al 2013, Hutchinson et al 2013, Sharma et al 2013). The correlation of stroke and HRQOL has also been previously demonstrated in non-surgical patients (Myint et al 2007). Preoperative quality of life has also been identified as a predictor of mortality after CABG up to 6 months postoperatively (Rumsfeld et al 1999, ter Horst). This study suggests that the predictive value of postoperative HRQOL extends further.

The finding that scores and changes, specifically on the VAS, predict or correlate with future morbidity suggest that a simple self-reported assessment of health and quality of life ranging from 0 to 100 is fairly indicative of later outcomes. Several studies on self-reported health as a predictor of outcomes (DeSalvo et al 2006, Miilunpalo et al 1997, Pietiläinen et al 2011) have reduced reporting to one question: "Generally speaking, how would you describe your health status: excellent, very good, good, fair, poor?". A reported less than good (i.e. fair or poor) health strongly predicted later disability and mortality in these studies. These findings suggest that a patient's subjective rating of diminished overall well-being is a red flag for clinicians and warrants further evaluation. A cheap and easily administered self-assessment tool such as the VAS could help focus costly screening methods and reduce expenditure for those most likely to be in their need.

All of the MACCE occurences in this study were acute in nature, meaning that they were not heralded by previous health care contacts. Predicting these events in patients who have undergone CABG is complicated; risk factors that are used for prediction in other populations (D'Agostino et al 2001) are already largely present. Risk factors specifically related to long term outcome after CABG have been identified, but they are mostly preoperative factors (Koch et al 2003, Wu et al 2012, Yoon et al 2013) making them consequently largely non-modifiable postoperatively. Additionally they do not explain a vast majority of poor long term outcomes (Filardo et al 2012), which alludes to the importance of preventing later new onset morbidity and on the other hand suggests the presence of unknown risk factors as pertinent to already known disease burden. Hence the assessment of changes in HRQOL offers a useful addition to the armamentarium of clinicians who treat coronary patients. The results of this study are limited by a small patient population, which warrants further validation and identification of cutoff values with larger study groups and possibly prospective registries.

7. CONCLUSIONS

Based on our studies on short and long-term outcome after coronary interventions, we conclude the following:

1. The use of blood products after coronary artery bypass grafting has a clear dose-dependent association with the risk of postoperative stroke and especially when solvent/detergent treated plasma and platelets are administered

2. Octogenarians with CAD treated with CABG have a better survival than those treated with PCI. When adjusted for important risk factors PCI and CABG confer similar survival rates

3. Mid-term outcome in patients on oral warfarin for AF is significantly better after CABG than PCI and the difference is driven by an increased risk of mortality and revascularization and not thromboembolic or bleeding events

4. CABG offers a significant improvement in HRQOL as measured by EQ5D at 6 months compared to baseline values and a decline in function and VAS on EQ5D and 6 month VAS values predict later MACCE –events

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REFERENCES

CASS Investigators 1984 “Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and nonrandomized patients meeting randomization criteria”, 1984, *Journal of the American College of Cardiology,* vol. 3, no. 1, pp. 114-128.

The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group 1984 “Eleven-Year Survival in the Veterans Administration Randomized Trial of Coronary Bypass Surgery for Stable Angina”, 1984, *New England Journal of Medicine,* vol. 311, no. 21, pp. 1333-1339.

European Coronary Surgery Study Group 1982 “LONG-TERM RESULTS OF PROSPECTIVE RANDOMISED STUDY OF CORONARY ARTERY BYPASS SURGERY IN STABLE ANGINA PECTORIS: European Coronary Surgery Study Group”, 1982, *The Lancet,* vol. 320, no. 8309, pp. 1173-1180.

Abel, N.J., Rogal, G.J., Burns, P., Saunders, C.R. & Chamberlain, R.S. 2013, “Aortic valve replacement with and without coronary artery bypass graft surgery in octogenarians: is it safe and feasible?”, *Cardiology,* vol. 124, no. 3, pp. 163-173.

Acharjee S, Boden WE, Hartigan PM, Teo KK, Maron DJ, Sedlis SP, Kostuk W, Spertus JA, Dada M, Chaitman BR, Mancini GB, Weintraub WS. 2013, “Low levels of high-density lipoprotein cholesterol and increased risk of cardiovascular events in stable ischemic heart disease patients: A post-hoc analysis from the COURAGE Trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation).” *Journal of the American College of Cardiology*, vol. 62, no. 20, pp. 1826-33.

Ad N, Barnett SD, Haan CK, O’Brien SM, Milford-Beland S, Speir AM. 2009, “Does preoperative atrial fibrillation increase the risk for mortality and morbidity after coronary artery bypass grafting?” *The Journal of thoracic and cardiovascular surgery,* vol. 137, no. 4, pp. 901-6.

Afilalo, J., Mottillo, S., Eisenberg, M.J., Alexander, K.P., Noiseux, N., Perrault, L.P., Morin, J., Langlois, Y., Ohayon, S.M., Monette, J., Boivin, J., Shahian, D.M. & Bergman, H. 2012, “Addition of Frailty and Disability to Cardiac Surgery Risk Scores Identifies Elderly Patients at High Risk of Mortality or Major Morbidity”, *Circulation: Cardiovascular Quality and Outcomes,* vol. 5, no. 2, pp. 222-228.

Airaksinen, K.E.J., Biancari, F., Karjalainen, P., Mikkola, R., Kuttila, K., Porela, P., Laitio, T. & Lip, G.Y.H. 2011, “Safety of coronary artery bypass surgery during therapeutic oral anticoagulation”, *Thrombosis research,* vol. 128, no. 5, pp. 435-439.

Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, Voeltz MD, Chandna H, Ramaiah C, Brtko M, Cannon L, Dyke C, Liu T, Montalescot G, Manoukian SV, Prats J, Topol EJ; BRIDGE Investigators. 2012 “Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial.” *JAMA*, vol. 307, no. 3, pp. 265-74.

Annala, A.P., Karjalainen, P.P., Biancari, F., Niemela, M., Ylitalo, A., Vikman, S., Porela, P. & Airaksinen, K.E. 2012, “Long-term safety of drug-eluting stents in patients on warfarin treatment”, *Annals of Medicine,* May;44(3):271-8.

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. 2008, “Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition).” *Chest,* vol. 133(6 Suppl), pp.160S-198S.

Antithrombotic Trialists’ Collaboration. 2002, “Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients.” *British Medical Journal,* no. 324, pp. 71–86

Antman, E.M., Hand, M., Armstrong, P.W., Bates, E.R., Green, L.A., Halasyamani, L.K., Hochman, J.S., Krumholz, H.M., Lamas, G.A., Mullany, C.J., Pearle, D.L., Sloan, M.A. & Smith JR, S.C. 2008, “2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction”, *Journal of the American College of Cardiology,* vol. 51, no. 2, pp. 210-247.

Attaran, S., Shaw, M., Bond, L., Pullan, M.D. & Fabri, B.M. 2011, “A Comparison of Outcome in Patients With Preoperative Atrial Fibrillation and Patients in Sinus Rhythm”, *The Annals of Thoracic Surgery,* vol. 92, no. 4, pp. 1391-1395.

Austin, P.C. 2011, “Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies." *Pharmaceutical Statistics,* 10(2), pp. 150-161.

Bagnall, N.M., Faiz, O., Darzi, A. & Athanasiou, T. 2013, "What is the utility of preoperative frailty assessment for risk stratification in cardiac surgery?", *Interactive CardioVascular and Thoracic Surgery,* vol. 17, no. 2, pp. 398-402.

Bagnall, N.M., Faiz, O., Darzi, A. & Athanasiou, T. 2013, "What is the utility of preoperative frailty assessment for risk stratification in cardiac surgery?", *Interactive CardioVascular and Thoracic Surgery,* vol. 17, no. 2, pp. 398-402.

Baig, K., Harling, L., Papanikitas, J., Attaran, S., Ashrafian, H., Casula, R. & Athanasiou, T. 2013, "Does coronary artery bypass grafting improve quality of life in elderly patients?", *Interactive CardioVascular and Thoracic Surgery,* vol. 17, no. 3, pp. 542-553.

BARI Investigators 1996 "Comparison of Coronary Bypass Surgery with Angioplasty in Patients with Multivessel Disease", 1996, *New England Journal of Medicine,* vol. 335, no. 4, pp. 217-225.

BARIinvestigators 2007, "The Final 10-Year Follow-Up Results From the BARI Randomized Trial", *Journal of the American College of Cardiology,* vol. 49, no. 15, pp. 1600-1606.

Bartnes, K., Hermansen, S.E., Dahl-Eriksen, Ø., Bahar, R., Busund, R., Sørlie, D.G. & Myrmel, T. 2013, "Arterial grafts do not counteract target vessel occlusion", *European Journal of Cardio-Thoracic Surgery,* vol. 44, no. 5, pp. e320-e324.

Batsis, J. & Lopez-Jimenez, F. 2010, "Cardiovascular risk assessment - From individual risk prediction to estimation of global risk and change in risk in the population", *BMC Medicine,* vol. 8, no. 1, pp. 29.

Benjamin, E.J., Wolf, P.A., D'Agostino, R.B., Silbershatz, H., Kannel, W.B. & Levy, D. 1998, "Impact of Atrial Fibrillation on the Risk of Death: The Framingham Heart Study", *Circulation,* vol. 98, no. 10, pp. 946-952.

Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. 2006, "Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials." *JAMA*, vol. 295,no. 3, pp. 306-13. Erratum in: *JAMA*, vol. 295, no. 17, p. 2002

Berger JS, Sallum RH, Katona B, Maya J, Ranganathan G, Xu Y, Mwamburi M. 2012, "Is there an association between aspirin dosing and cardiac and bleeding events after treatment of acute coronary syndrome? A systematic review of the literature." *American Heart Journal*, vol. 164, no. 2,pp. 153-162.e5.

Berghöfer A, Pischon T, Reinhold T, Apovian CM, Sharma AM, Willich SN. 2008, "Obesity prevalence from a European perspective: a systematic review." *BMC Public Health*. vol. 5, no.8, p200.

Biancari, F., Myllyla, M., Lepojarvi, S., Kuttila, K., Porela, P., Laitio, T., Ylitalo, A., Jokinen, V., Luokkala, A. & Airaksinen, K.E. 2010, "Preoperative warfarin treatment and outcome of coronary artery bypass graft surgery", *The Annals of Thoracic Surgery,* vol. 89, no. 4, pp. 1139-1145.

Biancari, F., Myllyla, M., Porela, P., Laitio, T., Kuttila, K., Satta, J., Lepojarvi, M., Juvonen, T. & Airaksinen, J.K. 2011, "Postoperative stroke in patients on oral anticoagulation undergoing coronary artery bypass surgery", *Scandinavian Cardiovascular Journal,* vol. 45, no. 6, pp. 360-8.

Biancari F, Onorati F, Faggian G, Heikkinen J, Anttila V, Jeppsson A, Mignosa C, Rubino AS, Gunn J, Wistbacka JO, Axelsson TA, Mennander A, De Feo M, Gudbjartsson T, Airaksinen J. 2014 "Determinants of outcome after isolated coronary artery bypass grafting in patients aged ≤50 years (from the Coronary aRtery diseAse in younG adultS study)". *American Journal of Cardiology*. 2014 Jan 15;113(2):275-8.

Biancari F, Vasques F, Mikkola R, Martin M, Lahtinen J, Heikkinen J. 2012, "Validation of EuroSCORE II in patients undergoing coronary artery bypass surgery." *The Annals of Thoracic Surgery*, vol. 93, no. 6, pp. 1930-5.

Biondi-Zoccai G, Romagnoli E, Castagno D, Sheiban I, De Servi S, Tamburino C, Colombo A, Burzotta F, Presbitero P, Bolognese L, Paloscia L, Rubino P, Sardella G, Briguori C, Niccoli L, Franco G, Di Girolamo D, Piatti L, Greco C, Petronio AS, Loi B, Benassi A, Patti A, Gaspardone A, Frati G, Sangiorgi G. 2012, "Simplifying clinical risk prediction for percutaneous coronary intervention of bifurcation lesions: the case for the ACEF (age, creatinine, ejection fraction) score." *EuroIntervention*, vol. 8, no. 3, pp. 359-67.

Boden, W.E., O'Rourke, R.A., Teo, K.K., Hartigan, P.M., Maron, D.J., Kostuk, W.J., Knudtson, M., Dada, M., Casperson, P., Harris, C.L., Chaitman, B.R., Shaw, L., Gosselin, G., Nawaz, S., Title, L.M., Gau, G., Blaustein, A.S., Booth, D.C., Bates, E.R., Spertus, J.A., Berman, D.S., Mancini, G.B.J. & Weintraub, W.S. 2007, "Optimal Medical Therapy with or without PCI for Stable Coronary Disease", *New England Journal of Medicine,* vol. 356, no. 15, pp. 1503-1516.

Bramer, S., van Straten, A.H.M., Soliman Hamad, M.A., Berreklouw, E., Martens, E.J. & Maessen, J.G. 2010, "The impact of preoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting", *European Journal of Cardio-Thoracic Surgery,* vol. 38, no. 3, pp. 373-379.

Braunwald, E., Antman, E.M., Beasley, J.W., Califf, R.M., Cheitlin, M.D., Hochman, J.S., Jones, R.H., Kereiakes, D., Kupersmith, J., Levin, T.N., Pepine, C.J., Schaeffer, J.W., Smith, E.E., Steward, D.E., Theroux, P., Task Force Members, Gibbons, R.J., Alpert, J.S., Eagle, K.A., Faxon, D.P., Fuster, V., Gardner, T.J., Gregoratos, G., Russell, R.O. & Smith, S.C. 2000, "ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction: Executive Summary and Recommendations: A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina)", *Circulation,* vol. 102, no. 10, pp. 1193-1209.

Bravell, M.E., Berg, S. & Malmberg, B. 2008, "Health, functional capacity, formal care, and survival in the oldest old: A longitudinal study", *Archives of Gerontology and Geriatrics,* vol. 46, no. 1, pp. 1-14.

Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. 2004, "Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features." *Circulation*, vol. 109, no. 19, pp. 2290-5.

Brener SJ, Oldroyd KG, Maehara A, El-Omar M, Witzenbichler B, Xu K, Mehran R, Gibson CM, Stone GW. 2014, "Outcomes in Patients With ST-Segment Elevation Acute Myocardial Infarction Treated With Clopidogrel Versus Prasugrel (from the INFUSE-AMI Trial)." *American Journal of Cardiology* [Epub ahead of print]

British Heart Foundation. 2010, "Coronary heart disease statistics 2010."www.bhf.org.uk

Buffolo E, de Andrade CS, Branco JN, Teles CA, Aguiar LF, Gomes WJ. 1996, "Coronary artery bypass grafting without cardiopulmonary bypass." *The Annals of Thoracic Surgery*. vol. 61,no.1, pp.63-6.

Caceres, M., Cheng, W., De Robertis, M., Mirocha, J.M., Czer, L., Esmailian, F., Khoynezhad, A., Ramzy, D., Kass, R. & Trento, A. 2013, "Survival and quality of life for nonagenarians after cardiac surgery", *The Annals of Thoracic Surgery,* vol. 95, no. 5, pp. 1598-1602.

Cameron, A., Davis, K.B., Green, G. & Schaff, H.V. 1996, "Coronary Bypass Surgery with Internal-Thoracic-Artery Grafts — Effects on Survival over a 15-Year Period", *New England Journal of Medicine,* vol. 334, no. 4, pp. 216-220.

Campo G, Guastaroba P, Marzocchi A, Santarelli A, Varani E, Vignali L, Sangiorgio P, Tondi S, Serenelli C, De Palma R, Saia F. 2013, "Impact of COPD on long-term outcome after ST-segment elevation myocardial infarction receiving primary percutaneous coronary intervention." *Chest*, vol. 144, no. 3, pp. 750-7.

Capewell S, Ford ES, Croft JB, Critchley JA, Greenlund KJ, Labarthe DR. 2010, "Cardiovascular risk factor trends and potential for reducing coronary heart disease mortality in the United States of America." *Bull World Health Organ*. vol. 88, no.2, pp.120-30.

Capodanno D, Caggegi A, Miano M, Cincotta G, Dipasqua F, Giacchi G, Capranzano P, Ussia G, Di Salvo ME, La Manna A, Tamburino C. 2011, "Global risk classification and clinical SYNTAX (synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) score in patients undergoing percutaneous or surgical left main revascularization." *JACC Cardiovascular Interventions,* vol. 4, no. 3, pp. 287-97.

Carrel, A. 1910, "VIII. On the Experimental Surgery of the Thoracic Aorta and Heart." *Annals of Surgery* 1910;52:83-95.

Cella DF. 1995, "Measuring quality of life in palliative care." *Seminars in Oncology*, vol. 22(2 Suppl 3), pp. 73-81.

Chapa, D.W., Akintade, B., Schron, E., Friedmann, E. & Thomas, S.A. 2013, "Is Health-Related Quality of Life a Predictor of Hospitalization or Mortality Among Women or Men with Atrial Fibrillation?", *The Journal of cardiovascular nursing,* . 2013 Oct 24. [Epub ahead of print]

Chelemer, S.B., Prato, B.S., Cox Jr., P.M., O'Connor, G.T. & Morton, J.R. 2002, "Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery", *Annals of Thoracic Surgery,* vol. 73, no. 1, pp. 138-142.

Cohen, D.J., Van Hout, B., Serruys, P.W., Mohr, F.W., Macaya, C., den Heijer, P., Vrakking, M.M., Wang, K., Mahoney, E.M., Audi, S., Leadley, K., Dawkins, K.D. & Kappetein, A.P. 2011, "Quality of Life after PCI with Drug-Eluting Stents or Coronary-Artery Bypass Surgery", *New England Journal of Medicine,* vol. 364, no. 11, pp. 1016-1026.

D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. 2001, "Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation." *JAMA*, vol. 286, no. 2, pp. 180-7.

Damiano, R.J.,Jr, Badhwar, V., Acker, M.A., Veeragandham, R.S., Kress, D.C., Robertson, J.O. & Sundt, T.M. 2014, "The CURE-AF trial: A prospective, multicenter trial of irrigated radiofrequency ablation for the treatment of persistent atrial fibrillation during concomitant cardiac surgery", *Heart rhythm : the official journal of the Heart Rhythm Society,* vol. 11, no. 1, pp. 39-45.

Daniels, R., van Rossum, E., Beurskens, A., van den Heuvel, W. & de Witte, L. 2012, "The predictive validity of three self-report screening instruments for identifying frail older people in the community", *BMC public health,* vol. 12, pp. 69-2458-12-69.

Dashwood, M.R., Dooley, A., Shi-Wen, X., Abraham, D.J. & Souza, D.S. 2007, "Does periadventitial fat-derived nitric oxide play a role in improved saphenous vein graft patency in patients undergoing coronary artery bypass surgery?", *Journal of vascular research,* vol. 44, no. 3, pp. 175-181.

Dashwood, M.R., Savage, K., Tsui, J.C.S., Dooley, A., Shaw, S.G., Fernández Alfonso, M.S., Bodin, L. & Souza, D.S.R. 2009, "Retaining perivascular tissue of human saphenous vein grafts protects against surgical and distension-induced damage and preserves endothelial nitric oxide synthase and nitric oxide synthase activity", *The Journal of thoracic and cardiovascular surgery,* vol. 138, no. 2, pp. 334-340.

De Aguiar, S.S., Bergmann, A. & Mattos, I.E. 2013, "Quality of life as a predictor of overall survival after breast cancer treatment", *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation,* .

De Bruyne, B., Pijls, N.H.J., Kalesan, B., Barbato, E., Tonino, P.A.L., Piroth, Z., Jagic, N., Möbius-Winkler, S., Rioufol, G., Witt, N., Kala, P., MacCarthy, P., Engström, T., Oldroyd, K.G., Mavromatis, K., Manoharan, G., Verlee, P., Frobert, O., Curzen, N., Johnson, J.B., Jüni, P. & Fearon, W.F. 2012, "Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease", *New England Journal of Medicine,* vol. 367, no. 11, pp. 991-1001.

DeFilippis, A.P., Blaha, M.J., Ndumele, C.E., Budoff, M.J., Lloyd-Jones, D.M., McClelland, R.L., Lakoski, S.G., Cushman, M., Wong, N.D., Blumenthal, R.S., Lima, J. & Nasir, K. 2011, "The Association of Framingham and Reynolds Risk Scores With Incidence and Progression of Coronary Artery Calcification in MESA (Multi-Ethnic Study of Atherosclerosis)", *Journal of the American College of Cardiology,* vol. 58, no. 20, pp. 2076-2083.

DeSalvo, K.B., Bloser, N., Reynolds, K., He, J. & Muntner, P. 2006, "Mortality Prediction with a Single General Self-Rated Health Question", *Journal of General Internal Medicine,* vol. 21, no. 3, pp. 267-275.

De Smedt, D., Clays, E., Annemans, L., Doyle, F., Kotseva, K., Pajak, A., Prugger, C., Jennings, C., Wood, D. & De Bacquer, D. 2013, "Health related quality of life in coronary patients and its association with their cardiovascular risk profile: results from the EUROASPIRE III survey", *International journal of cardiology,* vol. 168, no. 2, pp. 898-903.

Deutsch, M.A., Krane, M., Schneider, L., Wottke, M., Kornek, M., Elhmidi, Y., Badiu, C.C., Bleiziffer, S., Voss, B. & Lange, R. "Health-Related Quality of Life and Functional Outcome in Cardiac Surgical Patients Aged 80 Years and Older: A Prospective Single Center Study", *Journal of cardiac surgery,* 2014 Jan;29(1):14-21.

Dewilde, W.J., Oirbans, T., Verheugt, F.W., Kelder, J.C., De Smet, B.J., Herrman, J., Adriaenssens, T., Vrolix, M., Heestermans, A.A., Vis, M.M., Tijsen, J.G., van 't Hof, A.W. & ten Berg, J.M. "Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial", *The Lancet,* vol. 381, no. 9872, pp. 1107-1115.

DiMarco, J.P., Flaker, G., Waldo, A.L., Corley, S.D., Greene, H.L., Safford, R.E., Rosenfeld, L.E., Mitrani, G. & Nemeth, M. 2005, "Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: Observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study", *American Heart Journal,* vol. 149, no. 4, pp. 650-656.

Djärv T, Lagergren P. 2011, "Six-month postoperative quality of life predicts long-term survival after esophageal cancer surgery." *European Journal of Cancer*, vol. 47, no. 4, pp. 530-5.

Dorsam RT, Kunapuli SP. 2004, "Central role of the P2Y12 receptor in platelet activation." *Journal of Clinical Invesigationt*, vol. 113, no. 3, pp. 340-5.

Dotter, C.T. & Judkins, M.P. 1964, "Transluminal Treatment of Arteriosclerotic Obstruction. Description of a New Technic and a Preliminary Report of its Application", *Circulation,* vol. 30, pp. 654-670.

Dukkipati, S., O'Neill, W.W., Harjai, K.J., Sanders, W.P., Deo, D., Boura, J.A., Bartholomew, B.A., Yerkey, M.W., Sadeghi, H.M. & Kahn, J.K. 2004, "Characteristics of cerebrovascular accidents after percutaneous coronary interventions", *Journal of the American College of Cardiology,* vol. 43, no. 7, pp. 1161-1167.

Eikelboom, J.W., Mehta, S.R., Anand, S.S., Xie, C., Fox, K.A.A. & Yusuf, S. 2006, "Adverse Impact of Bleeding on Prognosis in Patients With Acute Coronary Syndromes", *Circulation,* vol. 114, no. 8, pp. 774-782.

Ekerstad, N., Swahn, E., Janzon, M., Alfredsson, J., Lofmark, R., Lindenberger, M. & Carlsson, P. 2011, "Frailty Is Independently Associated With Short-Term Outcomes for Elderly Patients With Non–ST-Segment Elevation Myocardial Infarction", *Circulation,* vol. 124, no. 22, pp. 2397-2404.

Ellis JJ, Eagle KA, Kline-Rogers EM, Erickson SR. 2005, "Validation of the EQ-5D in patients with a history of acute coronary syndrome." *Current medical research and opinion*, vol. 21, no. 8, pp. 1209-16.

El Solh, A.A., Bhora, M., Pineda, L. & Dhillon, R. 2006, "Nosocomial pneumonia in elderly patients following cardiac surgery", *Respiratory medicine,* vol. 100, no. 4, pp. 729-736.

Engoren, M.C., Habib, R.H., Zacharias, A., Schwann, T.A., Riordan, C.J. & Durham, S.J. 2002, "Effect of blood transfusion on long-term survival after cardiac operation", *Annals of Thoracic Surgery,* vol. 74, no. 4, pp. 1180-1186.

Enomoto, Y., Iijima, R., Tokue, M., Ito, N., Nagashima, Y., Araki, T., Yamazaki, K., Utsunomiya, M., Hori, M., Itaya, H., Shiba, M., Hara, H., Nakamura, M. & Sugi, K. 2013, "Bleeding risk with triple antithrombotic therapy in patients with atrial fibrillation and drug-eluting stents", *Cardiovascular intervention and therapeutics,* . 2013 Dec 24. [Epub ahead of print]

Farkouh, M.E., Domanski, M., Sleeper, L.A., Siami, F.S., Dangas, G., Mack, M., Yang, M., Cohen, D.J., Rosenberg, Y., Solomon, S.D., Desai, A.S., Gersh, B.J., Magnuson, E.A., Lansky, A., Boineau, R., Weinberger, J., Ramanathan, K., Sousa, J.E., Rankin, J., Bhargava, B., Buse, J., Hueb, W., Smith, C.R., Muratov, V., Bansilal, S., King, S., Bertrand, M. & Fuster, V. 2012, "Strategies for Multivessel Revascularization in Patients with Diabetes", *New England Journal of Medicine,* vol. 367, no. 25, pp. 2375-2384.

Farooq, V., Serruys, P.W., Garcia-Garcia, H.M., Zhang, Y., Bourantas, C.V., Holmes, D.R., Mack, M., Feldman, T., Morice, M.C., Stahle, E., James, S., Colombo, A., Diletti, R., Papafaklis, M.I., de Vries, T., Morel, M.A., van Es, G.A., Mohr, F.W., Dawkins, K.D., Kappetein, A.P., Sianos, G. & Boersma, E. 2013a, "The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial", *Journal of the American College of Cardiology,* vol. 61, no. 3, pp. 282-294.

Farooq, V., Serruys, P.W., Zhang, Y., Mack, M., Stahle, E., R., Holmes, D., Feldman, T., Morice, M., Colombo, A., Bourantas, C.V., de Vries, T., Morel, M., Ddawkins, K., Kappetein, A. & Mohr, F.W. 2013b, "Short and Long Term Clinical Impact of Stent Thrombosis and Graft Occlusion in the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery Trial: The SYNTAX Trial at 5 years", *Journal of the American College of Cardiology,vol.* 62, no. 25, pp. 2360-9.

Favaloro, R.G. 1969, "Saphenous vein graft in the surgical treatment of coronary artery disease. Operative technique", *The Journal of thoracic and cardiovascular surgery,* vol. 58, no. 2, pp. 178-185.

Feit, F., Brooks, M.M., Sopko, G., Keller, N.M., Rosen, A., Krone, R., Berger, P.B., Shemin, R., Attubato, M.J., Williams, D.O., Frye, R., Detre, K.M. & for the BARI Investigators 2000, "Long-Term Clinical Outcome in the Bypass Angioplasty Revascularization Investigation Registry: Comparison With the Randomized Trial", *Circulation,* vol. 101, no. 24, pp. 2795-2802.

Fihn, S.D., Gardin, J.M., Abrams, J., Berra, K., Blankenship, J.C., Dallas, A.P., Douglas, P.S., Foody, J.M., Gerber, T.C., Hinderliter, A.L., King, S.B.,3rd, Kligfield, P.D., Krumholz, H.M., Kwong, R.Y., Lim, M.J., Linderbaum, J.A., Mack, M.J., Munger, M.A., Prager, R.L., Sabik, J.F., Shaw, L.J., Sikkema, J.D., Smith, C.R.,Jr, Smith, S.C.,Jr, Spertus, J.A., Williams, S.V., Anderson, J.L. & American College of Cardiology Foundation/American Heart Association Task Force 2012, "2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons", *Circulation,* vol. 126, no. 25, pp. e354-471.

Filardo, G., Hamilton, C., Grayburn, P.A., Xu, H., Hebeler Jr, R.F. & Hamman, B. 2012, "Established Preoperative Risk Factors Do Not Predict Long-Term Survival in Isolated Coronary Artery Bypass

Grafting Patients", *The Annals of Thoracic Surgery,* vol. 93, no. 6, pp. 1943-1948.

Fischman, D.L., Leon, M.B., Baim, D.S., Schatz, R.A., Savage, M.P., Penn, I., Detre, K., Veltri, L., Ricci, D. & Nobuyoshi, M. 1994, "A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators", *The New England journal of medicine,* vol. 331, no. 8, pp. 496-501.

Ford, E.S., Ajani, U.A., Croft, J.B., Critchley, J.A., Labarthe, D.R., Kottke, T.E., Giles, W.H. & Capewell, S. 2007, "Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000", *New England Journal of Medicine,* vol. 356, no. 23, pp. 2388-2398.

Freedman MD. 1992, "Oral anticoagulants: pharmacodynamics, clinical indications and adverse effects." *Journal of Clinical Pharmacology*, vol. 32, no. 3, pp. 196-209

Fries, J.F. 2005, "Frailty, Heart Disease, and Stroke: The Compression of Morbidity Paradigm", *American Journal of Preventive Medicine,* vol. 29, no. 5, Supplement 1, pp. 164-168.

Fukahara, K., Kotoh, K., Doi, T., Misaki, T. & Sumi, S. 2010, "Impact of preoperative atrial fibrillation on the late outcome of off-pump coronary artery bypass surgery", *European Journal of Cardio-Thoracic Surgery,* vol. 38, no. 3, pp. 366-372.

Gage B.F., Waterman A.D., Shannon W., Boechler M., Rich M.W., Radford M.J. 2001, "Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation". *JAMA,* vol. 285, no. 22, pp. 2864–70.

Gao, Z., Xu, B., Yang, Y.J., Yuan, J.Q., Chen, J., Chen, J.L., Qiao, S.B., Wu, Y.J., Yan, H.B. & Gao, R.L. 2013, "Long-term outcomes of complete versus incomplete revascularization after drug-eluting stent implantation in patients with multivessel coronary disease", *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions,* vol. 82, no. 3, pp. 343-349.

Garrett H, Dennis EW,DeBakey ME 1973, "Aortocoronary bypass with saphenous vein graft: Seven-year follow-up", *JAMA,* vol. 223, no. 7, pp. 792-794.

Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. 2004, "Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization." *New England Journal of Medicine,* vol. 351, no. 13, pp. 1296-305.

Go AS, Hylek EM, Phillips KA,et al 2001, "Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (atria) study", *JAMA,* vol. 285, no. 18, pp. 2370-2375.

Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. 2003, "Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice?" *JAMA,* vol. 290, no. 20, pp. 2685-92.

Gould, K.L. & Lipscomb, K. 1974a, "Effects of coronary stenoses on coronary flow reserve and resistance", *The American Journal of Cardiology,* vol. 34, no. 1, pp. 48-55.

Gould, K.L., Lipscomb, K. & Hamilton, G.W. 1974b, "Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve", *The American Journal of Cardiology,* vol. 33, no. 1, pp. 87-94.

Green, G.E., Spencer, F.C., Tice, D.A. & Stertzer, S.H. 1970, "Arterial and venous microsurgical bypass grafts for coronary artery disease", *The Journal of thoracic and cardiovascular surgery,* vol. 60, no. 4, pp. 491-503.

Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, Hawkey M, Maurer MS, Kirtane AJ, Kodali S, Moses JW, Leon MB, Smith CR, Williams M. 2012, "The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience." *JACC Cardiovascular Interventions* ,vol. 5, no. 9, pp. 974-81.

Griffo R, Ambrosetti M, Tramarin R, Fattirolli F, Temporelli PL, Vestri AR, De Feo S, Tavazzi L; ICAROS investigators. 2013, "Effective secondary prevention through cardiac rehabilitation after coronary revascularization and predictors of poor adherence to lifestyle modification and medication. Results of the ICAROS Survey." *International Journal of Cardiology,* vol. 167, no. 4, pp. 1390-5.

Grothusen, C., Attmann, T., Friedrich, C., Freitag-Wolf, S., Haake, N., Cremer, J. & Schottler, J. 2013, "Predictors for long-term outcome and quality of life of patients after cardiac surgery with prolonged intensive care unit stay", *Interventional medicine & applied science,* vol. 5, no. 1, pp. 3-9.

Grover FL, Shroyer AL, Edwards FH, Pae WE Jr, Ferguson TB Jr, Gay WA Jr, Clark RE. 1996, "Data quality review program: the Society of Thoracic Surgeons Adult Cardiac National Database." *The*

Annals of Thoracic Surgery, vol. 62, no. 4, pp. 1229-31.

Gruntzig, A.R., Senning, A. & Siegenthaler, W.E. 1979, "Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty", *The New England journal of medicine,* vol. 301, no. 2, pp. 61-68.

Guptill, J.T., Mehta, R.H., Armstrong, P.W., Horton, J., Laskowitz, D., James, S., Granger, C.B. & Lopes, R.D. 2013, "Stroke After Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction: Timing, Characteristics, and Clinical Outcomes", *Circulation: Cardiovascular Interventions,* vol. 6, no. 2, pp. 176-183.

Guyatt GH, Feeny DH, Patrick DL. 1993, "Measuring health-related quality of life." *Annals of Internal Medicine*, vol. 118, pp. 622-628.

Hamm, C.W., Bassand, J.P., Agewall, S., Bax, J., Boersma, E., Bueno, H., Caso, P., Dudek, D., Gielen, S., Huber, K., Ohman, M., Petrie, M.C., Sonntag, F., Uva, M.S., Storey, R.F., Wijns, W., Zahger, D. & ESC Committee for Practice Guidelines 2011, "ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)", *European heart journal,* vol. 32, no. 23, pp. 2999-3054.

Hannan EL, Cozzens K, King SB, III, Walford G, Shah NR. 2012, "The New York State Cardiac Registries: History, Contributions, Limitations, and Lessons for Future Efforts to Assess and Publicly Report Healthcare Outcomes." *Journal of the American College of Cardiology,* vol. 59, no. 25, pp. 2309-2316.

Hansen, M.L., Sorensen, R., Clausen, M.T., Fog-Petersen, M.L., Raunso, J., Gadsboll, N., Gislason, G.H., Folke, F., Andersen, S.S., Schramm, T.K., Abildstrom, S.Z., Poulsen, H.E., Kober, L. & Torp-Pedersen, C. 2010, "Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation", *Archives of Internal Medicine,* vol. 170, no. 16, pp. 1433-1441.

Hansson EC, Rexius H, Dellborg M, Albertsson P, Jeppsson A. 2014, "Coronary artery bypass grafting-related bleeding complications in real-life acute coronary syndrome patients treated with clopidogrel or ticagrelor." *European Journal of Cardiothoracic Surgery*, [Epub ahead of print]

Hart, R.G., Halperin, J.L., Pearce, L.A., Anderson, D.C., Kronmal, R.A., McBride, R., Nasco, E., Sherman, D.G., Talbert, R.L., Marler, J.R. & , 2003, "Lessons from the Stroke Prevention in Atrial Fibrillation Trials", *Annals of Internal Medicine,* vol. 138, no. 10, pp. 831-838.

Hart, R.G., Pearce, L.A., Rothbart, R.M., McAnulty, J.H., Asinger, R.W. & Halperin, J.L. 2000, "Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy", *Journal of the American College of Cardiology,* vol. 35, no. 1, pp. 183-187.

Hashemzadeh M, Goldsberry S, Furukawa M, Khoynezhad A, Movahed MR. 2009, "ADP receptor-blocker thienopyridines: chemical structures, mode of action and clinical use. A review." *Journal of Invasive Cardiology*, vol. 21, no.8, pp. 406-12.

Hashemzadeh, K. & Hashemzadeh, S. 2012, "Predictors and outcome of gastrointestinal complications after cardiac surgery", *Minerva chirurgica,* vol. 67, no. 4, pp. 327-335.

Hayward, P.A.R., Gordon, I.R., Hare, D.L., Matalanis, G., Horrigan, M.L., Rosalion, A. & Buxton, B.F. 2010, "Comparable patencies of the radial artery and right internal thoracic artery or saphenous vein beyond 5 years: Results from the Radial Artery Patency and Clinical Outcomes trial", *The Journal of thoracic and cardiovascular surgery,* vol. 139, no. 1, pp. 60-67.

Hearn, J.A., King, S.B.,3rd, Douglas, J.S.,Jr, Carlin, S.F., Lembo, N.J. & Ghazzal, Z.M. 1993, "Clinical and angiographic outcomes after coronary artery stenting for acute or threatened closure after percutaneous transluminal coronary angioplasty. Initial results with a balloon-expandable, stainless steel design", *Circulation,* vol. 88, no. 5 Pt 1, pp. 2086-2096.

Helgadottir, S., Sigurdsson, M., Ingvarsdottir, I., Arnar, D. & Gudbjartsson, T. 2012, "Atrial fibrillation following cardiac surgery: risk analysis and long-term survival", *Journal of Cardiothoracic Surgery,* vol. 7, no. 1, pp. 87.

Herman CR, Buth KJ, Kent BA, Hirsch GM. 2010, "Clopidogrel increases blood transfusion and hemorrhagic complications in patients undergoing cardiac surgery." The Annals of Thoracic Surgery vol. 89, no. 2, pp. 397-402.

Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. 1992, "Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients." *JAMA,* vol. 267, pp. 2344-2348.

Hoekstra, T., Jaarsma, T., van Veldhuisen, D.J., Hillege, H.L., Sanderman, R. & Lesman-Leegte, I. 2013, "Quality of life and survival in patients with heart failure", *European Journal of Heart Failure,* vol. 15, no. 1, pp. 94-102.

Hutchinson, A., Rasekaba, T.M., Graco, M., Berlowitz, D.J., Hawthorne, G. & Lim, W.K. 2013, "Relationship between health-related quality of life,and acute care re-admissions and survival in older adults with chronic illness", *Health and quality of life outcomes,* vol. 11, no. 1, pp. 136.

Hylek, E.M., Evans-Molina, C., Shea, C., Henault, L.E. & Regan, S. 2007, "Major Hemorrhage and Tolerability of Warfarin in the First Year of Therapy Among Elderly Patients With Atrial Fibrillation", *Circulation,* vol. 115, no. 21, pp. 2689-2696.

Jacobs JP, Jacobs ML, Maruszewski B, Lacour-Gayet FG, Clarke DR, Tchervenkov CI, Gaynor JW, Spray TL, Stellin G, Elliott MJ, Ebels T, Mavroudis C. 2005, "Current status of the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons Congenital Heart Surgery Database." *The Annals of Thoracic Surgery*, vol. 80, no. 6, pp. 2278-83.

Järvinen, O., Hokkanen, M. & Huhtala, H. 2013, "Quality of life 12 years after on-pump and off-pump coronary artery bypass grafting", *Coronary artery disease,* vol. 24, no. 8, pp. 663-668.

Johansson, B.L., Souza, D.S.R., Bodin, L., Filbey, D., Loesch, A., Geijer, H. & Bojö, L. 2010, "Slower progression of atherosclerosis in vein grafts harvested with 'no touch' technique compared with conventional harvesting technique in coronary artery bypass grafting: an angiographic and intravascular ultrasound study", *European Journal of Cardio-Thoracic Surgery,* vol. 38, no. 4, pp. 414-419.

Jokinen, J.J., Hippeläinen, M.J., Turpeinen, A.K., Pitkänen, O. & Hartikainen, J.E.K. 2010, "Health-Related Quality of Life After Coronary Artery Bypass Grafting: A Review of Randomized Controlled Trials", *Journal of cardiac surgery,* vol. 25, no. 3, pp. 309-317.

Kannel W.B., Dawber T.R., Kagan A. & Revotskie 1961, "Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up ExperienceThe Framingham Study", *Annals of Internal Medicine,* vol. 55, no. 1, pp. 33-50.

Kaplan NM. 1989, "The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension." *Archives of Internal Medicine*, vol. 149, no. 7, pp. 1514-20.

Karjalainen, P.P., Porela, P., Ylitalo, A., Vikman, S., Nyman, K., Vaittinen, M., Airaksinen, T.J., Niemelä, M., Vahlberg, T. & Airaksinen, K.E.J. 2007, "Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting", *European heart journal,* vol. 28, no. 6, pp. 726-732.

Karkouti, K., Wijeysundera, D.N. & Beattie, W.S. 2008, "Risk associated with preoperative anemia in cardiac surgery : A multicenter cohort study", *Circulation,* vol. 117, no. 4, pp. 478-484.

Karkouti, K., Wijeysundera, D.N., Yau, T.M., McCluskey, S.A., Chan, C.T., Wong, P.-. & Beattie, W.S. 2011, "Influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients", *Anesthesiology,* vol. 115, no. 3, pp. 523-530.

Kastrati, A., Mehilli, J., Pache, J., Kaiser, C., Valgimigli, M., Kelbæk, H., Menichelli, M., Sabaté, M., Suttorp, M.J., Baumgart, D., Seyfarth, M., Pfisterer, M.E. & Schömig, A. 2007, "Analysis of 14 Trials Comparing Sirolimus-Eluting Stents with Bare-Metal Stents", *New England Journal of Medicine,* vol. 356, no. 10, pp. 1030-1039.

Kattainen, A., Salomaa, V., Härkänen, T., Jula, A., Kaaja, R., Kesäniemi, Y.A., Kahnen, M., Moilanen, L., Nieminen, M.S., Aromaa, A. & Reunanen, A. 2006, "Coronary heart disease: from a disease of middle-aged men in the late 1970s to a disease of elderly women in the 2000s", *European heart journal,* vol. 27, no. 3, pp. 296-301.

Kautiainen S, Rimpelä A, Vikat A, Virtanen SM. 2002, "Secular trends in overweight and obesity among Finnish adolescents in 1977-1999." *International journal of obesity and related metabolic disorders*. vol. 26, no.4, pp.544-52.

King III, S.B., Kosinski, A.S., Guyton, R.A., Lembo, N.J. & Weintraub, W.S. 2000, "Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST)", *Journal of the American College of Cardiology,* vol. 35, no. 5, pp. 1116-1121.

Kinjo, K., Sato, H., Sato, H., Ohnishi, Y., Hishida, E., Nakatani, D., Mizuno, H., Fukunami, M., Koretsune, Y., Takeda, H. & Hori, M. 2003, "Prognostic significance of atrial fibrillation/atrial flutter in patients with acute myocardial infarction treated with percutaneous coronary intervention", *The American Journal of Cardiology,* vol. 92, no. 10, pp. 1150-1154.

Kiviniemi, T., Karjalainen, P., Pietilä, M., Ylitalo, A., Niemelä, M., Vikman, S., Puurunen, M., Biancari, F. & Airaksinen, K.E.J. 2012, "Comparison of Additional Versus No Additional Heparin During Therapeutic Oral Anticoagulation in Patients Undergoing Percutaneous Coronary Intervention", *The American Journal of Cardiology,* vol. 110, no. 1, pp. 30-35.

Klein, B.E.K., Klein, R., Knudtson, M.D. & Lee, K.E. 2005, "Frailty, morbidity and survival", *Archives of Gerontology and Geriatrics,* vol. 41, no. 2, pp. 141-149.

Koch, C.G., Khandwala, F., Cywinski, J.B., Ishwaran, H., Estafanous, F.G., Loop, F.D. & Blackstone, E.H. 2004, "Health-related quality of life after coronary artery bypass grafting: A gender analysis using the Duke Activity Status Index", *The Journal of thoracic and cardiovascular surgery,* vol. 128, no. 2, pp. 284-295.

Koch, C.G., Weng, Y., Zhou, S.X., Savino, J.S., Mathew, J.P., Hsu, P.H., Saidman, L.J. & Mangano, D.T. 2003, "Prevalence of risk factors, and not gender per se, determines short- and long-term survival after coronary artery bypass surgery", *Journal of cardiothoracic and vascular anesthesia,* vol. 17, no. 5, pp. 585-593.

Kolesov, V. & Potashov, L. 1965, *[Surgery of coronary arteries]. Eksp Khir Anesteziol*. 1965 Mar-Apr;10(2):3-8.

Konstantinov IE. 2000, "Robert H. Goetz: the surgeon who performed the first successful clinical coronary artery bypass operation." *The Annals of Thoracic Surgery*. vol. 69, no.6, pp.1966-72.

Korn-Lubetzki, I., Farkash, R., Pachino, R.M., Almagor, Y., Tzivoni, D. & Meerkin, D. 2013, "Incidence and Risk Factors of Cerebrovascular Events Following Cardiac Catheterization", *Journal of the American Heart Association,* vol. 2, no. 6.

Krijthe, B.P., Kunst, A., Benjamin, E.J., Lip, G.Y.H., Franco, O.H., Hofman, A., Witteman, J.C.M., Stricker, B.H. & Heeringa, J. 2013, "Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060", *European heart journal,* vol. 34, no. 35, pp. 2746-2751.

Krumholz HM, Wang Y, Chen J,et al 2009, "Reduction in acute myocardial infarction mortality in the united states: Risk-standardized mortality rates from 1995-2006", *JAMA,* vol. 302, no. 7, pp. 767-773.

Kuduvalli, M., Oo, A.Y., Newall, N., Grayson, A.D., Jackson, M., Desmond, M.J., Fabri, B.M. & Rashid, A. 2005, "Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery", *European Journal of Cardio-thoracic Surgery,* vol. 27, no. 4, pp. 592-598.

Kunt AG, Kurtcephe M, Hidiroglu M, Cetin L, Kucuker A, Bakuy V, Akar AR, Sener E. 2013, "Comparison of original EuroSCORE, EuroSCORE II and STS risk models in a Turkish cardiac surgical cohort." *Interact Cardiovasc Thorac Surg*, vol. 16, no. 5, pp. 625-9.

Kurbaan, A.S., Bowker, T.J., Ilsley, C.D., Sigwart, U. & Rickards, A.F. 2001, "Difference in the mortality of the CABRI diabetic and nondiabetic populations and its relation to coronary artery disease and the revascularization mode", *The American Journal of Cardiology,* vol. 87, no. 8, pp. 947-950.

Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. 2010, "Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups." *The Annals of Thoracic Surgery*. vol. 90, no.1,pp. 101-8.

Lahtinen, J., Biancari, F., Salmela, E., Mosorin, M., Satta, J., Rainio, P., Rimpiläinen, J., Lepojärvi, M. & Juvonen, T. 2004, "Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery", *The Annals of Thoracic Surgery,* vol. 77, no. 4, pp. 1241-1244.

Leahy, M.J., Thurber, D. & Calvert Jr., J.F. 2005, "Benefits and challenges of research with the oldest old for participants and nurses", *Geriatric nursing,* vol. 26, no. 1, pp. 21-28.

Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. 2010, "Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery." *Circulation*, vol. 121, no. 8, pp. 973-8.

Lloyd-Jones, D.M., Wang, T.J., Leip, E.P., Larson, M.G., Levy, D., Vasan, R.S., D'Agostino, R.B., Massaro, J.M., Beiser, A., Wolf, P.A. & Benjamin, E.J. 2004, "Lifetime Risk for Development of Atrial Fibrillation: The Framingham Heart Study", *Circulation,* vol. 110, no. 9, pp. 1042-1046.

Locker, C., Schaff, H.V., Dearani, J.A., Joyce, L.D., Park, S.J., Burkhart, H.M., Suri, R.M., Greason, K.L., Stulak, J.M., Li, Z. & Daly, R.C. 2012, "Multiple arterial grafts improve late survival of patients undergoing coronary artery bypass graft surgery: analysis of 8622 patients with multivessel disease", *Circulation,* vol. 126, no. 9, pp. 1023-1030.

Loop, F.D., Lytle, B.W., Cosgrove, D.M., Stewart, R.W., Goormastic, M., Williams, G.W., Golding, L.A.R., Gill, C.C., Taylor, P.C., Sheldon, W.C. & Proudfit, W.L. 1986, "Influence of the Internal-Mammary-Artery Graft on 10-Year Survival and Other Cardiac Events", *New England Journal of Medicine,* vol. 314, no. 1, pp. 1-6.

Lopes, R.D., Elliott, L.E., White, H.D., Hochman, J.S., Van de Werf, F., Ardissino, D., Nielsen, T.T., Weaver, W.D., Widimsky, P., Armstrong, P.W. & Granger, C.B. 2009, "Antithrombotic therapy and outcomes of patients with atrial fibrillation following primary percutaneous coronary intervention: results from the APEX-AMI trial", *European heart journal,* vol. 30, no. 16, pp. 2019-2028.

Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T. & Murray, C.J. 2001, "Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data", *The Lancet,* vol. 367, no. 9524, pp. 1747-1757.

Loponen P, Luther M, Korpilahti K, Wistbacka JO, Huhtala H, Laurikka J, Tarkka MR. 2009, "HRQoL after coronary artery bypass grafting and percutaneous coronary intervention for stable angina." *Scandinavian Cardiovascular Journal*. vol. 43, no.2, pp. 94-9.

Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. 2004, "The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years." *The Annals of Thoracic Surgery*. vol. 78, no. 6, pp. 2005-12; discussion 2012-4

Lytle, B.W., Loop, F.D., Cosgrove, D.M., Ratliff, N.B., Easley, K. & Taylor, P.C. 1985, "Long-term (5 to 12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts", *The Journal of thoracic and cardiovascular surgery,* vol. 89, no. 2, pp. 248-258.

Maciejewski, M.L., Liu, C. & Fihn, S.D. 2009, "Performance of Comorbidity, Risk Adjustment, and Functional Status Measures in Expenditure Prediction for Patients With Diabetes", *Diabetes care,* vol. 32, no. 1, pp. 75-80.

Mancini GB, Hartigan PM, Shaw LJ, Berman DS, Hayes SW, Bates ER, Maron DJ, Teo K, Sedlis SP, Chaitman BR, Weintraub WS, Spertus JA, Kostuk WJ, Dada M, Booth DC, Boden WE. 2014, "Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia." *JACC Cardiovascular Interventions*, vol. 7, no. 2, pp. 195-201.

Markar SR, Low DE. 2013, "Physiology, not chronology, dictates outcomes after esophagectomy for esophageal cancer: outcomes in patients 80 years and older." *Annals of Surgical Oncology,* vol. 20, no. 3, pp. 1020-6

Mattila, P., Vento, A., Ristikankare, M. & Mattila, S. 1990, "Multivariate analysis of operative mortality and late outcome after coronary bypass surgery", *The Journal of cardiovascular surgery,* vol. 31, no. 2, pp. 220-224.

McGill HC, Jr., McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. 2000, "Origin of atherosclerosis in childhood and adolescence." *American journal of clinical nutrition,* vol. 72, pp.1307S-1315S.

McKellar, S.H., Brown, M.L., Frye, R.L., Schaff, H.V. & Sundt, T.M.,3rd 2008, "Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis", *Nature clinical practice.Cardiovascular medicine,* vol. 5, no. 11, pp. 738-746.

McManus, D.D., Gore, J., Yarzebski, J., Spencer, F., Lessard, D. & Goldberg, R.J. 2011, "Recent Trends in the Incidence, Treatment, and Outcomes of Patients with STEMI and NSTEMI", *The American Journal of Medicine,* vol. 124, no. 1, pp. 40-47.

Mehta, R.H., Dabbous, O.H., Granger, C.B., Kuznetsova, P., Kline-Rogers, E.M., Anderson Jr., F.A., Fox, K.A.A., Gore, J.M., Goldberg, R.J. & Eagle, K.A. 2003, "Comparison of outcomes of patients with acute coronary syndromes with and without atrial fibrillation", *The American Journal of Cardiology,* vol. 92, no. 9, pp. 1031-1036.

Metz, L.D., Beattie, M., Hom, R., Redberg, R.F., Grady, D. & Fleischmann, K.E. 2007, "The Prognostic Value of Normal Exercise Myocardial Perfusion Imaging and Exercise Echocardiography: A Meta-Analysis", *Journal of the American College of Cardiology,* vol. 49, no. 2, pp. 227-237.

Middel, B., El Baz, N., Pedersen, S.S., van Dijk, J.P., Wynia, K. & Reijneveld, S.A. 2013, "Decline in Health-Related Quality of Life 6 Months After Coronary Artery Bypass Graft Surgery: The Influence of Anxiety, Depression, and Personality Traits", *The Journal of cardiovascular nursing,* 2013 Oct 24. [Epub ahead of print].

Miilunpalo, S., Vuori, I., Oja, P., Pasanen, M. & Urponen, H. 1997, "Self-rated health status as a health measure: The predictive value of self-reported health status on the use of physician services and on mortality in the working-age population", *Journal of clinical epidemiology,* vol. 50, no. 5, pp. 517-528.

Mohr, F.W., Morice, M., Kappetein, A.P., Feldman, T.E., Ståhle, E., Colombo, A., Mack, M.J., Holmes Jr, D.R., Morel, M., Dyck, N.V., Houle, V.M., Dawkins, K.D. & Serruys, P.W. 2013, "Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial", *The Lancet,* vol. 381, no. 9867, pp. 629-638.

Movahed, M., John, J., Hashemzadeh, M., Jamal, M.M. & Hashemzadeh, M. 2009, "Trends in the Age Adjusted Mortality from Acute ST Segment Elevation Myocardial Infarction in the United

States (1988–2004) Based on Race, Gender, Infarct Location and Comorbidities", *The American Journal of Cardiology,* vol. 104, no. 8, pp. 1030-1034.

Murphy, G.J., Reeves, B.C., Rogers, C.A., Rizvi, S.I.A., Culliford, L. & Angelini, G.D. 2007, "Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery", *Circulation,* vol. 116, no. 22, pp. 2544-2552.

Mustonen, J., Kettunen, R., Kupari, M., Mäkikallio, T., Ylitalo, A. & Raatikainen, P. 2011, "Sydäntoimenpiteet Suomessa nyt ja tulevaisuudessa", *Suomen Lääkärilehti,* vol. 67, no. 19, pp. 152.

Myint, P.K., Surtees, P.G., Wainwright, N.W., Luben, R.N., Welch, A.A., Bingham, S.A., Wareham, N.J. & Khaw, K.T. 2007, "Physical health-related quality of life predicts stroke in the EPIC-Norfolk", *Neurology,* vol. 69, no. 24, pp. 2243-2248.

Nagelschmitz J, Blunck M, Kraetzschmar J, Ludwig M, Wensing G, Hohlfeld T. 2014, "Pharmacokinetics and pharmacodynamics of acetylsalicylic acid after intravenous and oral administration to healthy volunteers." *Clinical Pharmacology*, vol. 6, pp. 51-9.

Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. 2012, "EuroSCORE II." *European Journal of Cardiothoracic Surgery*, vol. 41, no. 4, pp. 734-44.

Ndrepepa G, Kastrati A. 2014, "Bleeding complications in patients undergoing percutaneous coronary interventions: current status and perspective." *Coronary Artery Disease*, vol. 25, no. 3, pp. 247-57.

Neyt M, Van Brabandt H, Devos C. 2013, "The cost-utility of catheter ablation of atrial fibrillation: a systematic review and critical appraisal of economic evaluations." *BMC Cardiovascular Disorders*, Sep 26;13:78.

Ngaage, D.L., Schaff, H.V., Mullany, C.J., Sundt III, T.M., Dearani, J.A., Barnes, S., Daly, R.C. & Orszulak, T.A. 2007, "Does preoperative atrial fibrillation influence early and late outcomes of coronary artery bypass grafting?", *The Journal of thoracic and cardiovascular surgery,* vol. 133, no. 1, pp. 182-189.

Nikus, K. 2007, "Mortality of patients with acute coronary syndromes still remains high: A follow-up study of 1188 consecutive patients admitted to a university hospital", *Annals of Medicine,* vol. 39, no. 1, pp. 63-71.

Ong, A.T.L. & Serruys, P.W. 2006, "Complete Revascularization: Coronary Artery Bypass Graft Surgery Versus Percutaneous Coronary Intervention", *Circulation,* vol. 114, no. 3, pp. 249-255.

Orford, J.L., Fasseas, P., Melby, S., Burger, K., Steinhubl, S.R., Holmes, D.R. & Berger, P.B. 2004, "Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation", *American Heart Journal,* vol. 147, no. 3, pp. 463-467.

Ouzounian, M., Hassan, A., Buth, K.J., MacPherson, C., Ali, I.M., Hirsch, G.M. & Ali, I.S. 2010, "Impact of Endoscopic Versus Open Saphenous Vein Harvest Techniques on Outcomes After Coronary Artery Bypass Grafting", *The Annals of Thoracic Surgery,* vol. 89, no. 2, pp. 403-408.

Palareti, G., Leali, N., Coccheri, S., Poggi, M., Manotti, C., D'Angelo, A., Pengo, V., Erba, N., Moia, M., Ciavarella, N., Devoto, G., Berrettini, M. & Musolesi, S. 1996, "Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT)", *The Lancet,* vol. 348, no. 9025, pp. 423-428.

Palmerini, T., Biondi-Zoccai, G., Riva, D.D., Mariani, A., Savini, C., Eusanio, M.D., Genereux, P., Frati, G., Marullo, A.G.M., Landoni, G., Greco, T., Branzi, A., Servi, S.D., Credico, G.D., Taglieri, N., Williams, M.R. & Stone, G.W. 2013, "Risk of stroke with percutaneous coronary intervention compared with on-pump and off-pump coronary artery bypass graft surgery: Evidence from a comprehensive network meta-analysis", *American Heart Journal,* vol. 165, no. 6, pp. 910-917.e14.

Parang, P. & Arora, R. 2009, "Coronary vein graft disease: pathogenesis and prevention", *The Canadian journal of cardiology,* vol. 25, no. 2, pp. e57-62.

Parsonnet V, Dean D, Bernstein AD. 1989, "A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease." *Circulation*, vol. 79, pp. I3-12.

Partridge, J.S.L., Harari, D. & Dhesi, J.K. 2012, "Frailty in the older surgical patient: a review", *Age and Ageing,* vol. 41, no. 2, pp. 142-147.

Patrono, C., Coller, B., FitzGerald, G.A., Hirsh, J., Roth, G. 2004, "Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy." *Chest*, vol. 126 (3 Suppl.), pp. 234S-264S.

Pattakos, G., Koch, C.G., Brizzio, M.E., Batizy, L.H., Sabik III, J.F., Blackstone, E.H. & Lauer, M.S. 2012, "Outcome of patients who refuse transfusion after cardiac surgery: A natural experiment with severe blood conservation", *Archives of Internal Medicine,* vol. 172, no. 15, pp. 1154-1160.

Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E, Di Sciascio G. 2006, "Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3(Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery)study." *Circulation*.vol. 114, no.14, pp.1455-61.

Perrin, N.A., Stiefel, M., Mosen, D.M., Bauck, A., Shuster, E. & Dirks, E.M. 2011, "Self-reported health and functional status information improves prediction of inpatient admissions and costs", *The American Journal of Managed Care,* vol. 17, no. 12, pp. e472-8.

Pick, A.W., Orszulak, T.A., Anderson, B.J. & Schaff, H.V. 1997, "Single versus bilateral internal mammary artery grafts: 10-year outcome analysis", *The Annals of Thoracic Surgery,* vol. 64, no. 3, pp. 599-605.

Pietiläinen O., Laaksonen M., Rahkonen O. & Lahelma E. 2011, "Self-Rated Health as a Predictor of Disability Retirement – The Contribution of Ill-Health and Working Conditions," – *PLoS One*, vol. 6, no. 9, e25004.

Pietinen, P., Nissinen, A., Vartiainen, E., Tuomilehto, A., Uusitalo, U., Ketola, A., Moisio, S. & Puska, P. 1988, "Dietary changes in the North Karelia Project (1972–1982)", *Preventive medicine,* vol. 17, no. 2, pp. 183-193.

Pijls, N.H.J., van Schaardenburgh, P., Manoharan, G., Boersma, E., Bech, J., van't Veer, M., Bär, F., Hoorntje, J., Koolen, J., Wijns, W. & de Bruyne, B. 2007, "Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis: 5-Year Follow-Up of the DEFER Study", *Journal of the American College of Cardiology,* vol. 49, no. 21, pp. 2105-2111.

Pijpers, E., Ferreira, I., Stehouwer, C.D.A. & Nieuwenhuijzen Kruseman, A.C. 2012, "The frailty dilemma. Review of the predictive accuracy of major frailty scores", *European journal of internal medicine,* vol. 23, no. 2, pp. 118-123.

Pocock, S.J., Henderson, R.A., Rickards, A.F., Hampton, J.R., King, S.B.,3rd, Hamm, C.W., Puel, J., Hueb, W., Goy, J.J. & Rodriguez, A. 1995, "Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery", *Lancet,* vol. 346, no. 8984, pp. 1184-1189.

Proietti, R., Santangeli, P., Di Biase, L., Joza, J., Bernier, M.L., Wang, Y., Sagone, A., Viecca, M., Essebag, V. & Natale, A. 2014, "Comparative Effectiveness of Wide Antral Versus Ostial Pulmonary Vein Isolation: A Systematic Review and Meta-Analysis", *Circulation: Arrhythmia and Electrophysiology,* 2014 Feb 1;7(1):39-45.

Puska, P. & Stahl, T. 2010, "Health in All Policies—The Finnish Initiative: Background, Principles, and Current Issues", *Annual Review of Public Health,* vol. 31, no. 1, pp. 315-328.

Raatikainen P, Huikuri H. 2008, "Eteisvärinän määritelmä ja luokitus." Published in: *Heikkilä J, Kupari M, Airaksinen J, Huikuri H, Nieminen MS, Peuhkurinen K, toim. Kardiologia. Jyväskylä: Kustannus Oy Duodecim 2008*, pp. 534-6.

Raja, S.G., Shah, J., Navaratnarajah, M., Amin, F. & Amrani, M. 2013, "Outcomes and predictors of mortality and stroke after on-pump and off-pump coronary artery bypass surgery in octogenarians", *Innovations (Philadelphia, Pa.),* vol. 8, no. 4, pp. 269-275.

Rensing BJ, Vos J, Smits PC, Foley DP, van den Brand MJ, van der Giessen WJ, de Feijter PJ, Serruys PW. 2001, "Coronary restenosis elimination with a sirolimus eluting stent: first European human experience with 6-month angiographic and intravascular ultrasonic follow-up." *European Heart Journal*, vol. 22, no. 22, pp. 2125-30.

Rittger, H., Rieber, J., Kogler, K., Sinha, A., Schmidt, M., Breithardt, O.A., Biggar, P., Einsle, F., Diegeler, A. & Brachmann, J. 2011, "Clinical outcome and quality of life after interventional treatment of left main disease with drug-eluting-stents in comparison to CABG in elderly and younger patients", *Clinical research in cardiology : official journal of the German Cardiac Society,* vol. 100, no. 5, pp. 439-446.

Rogacka, R., Chieffo, A., Michev, I., Airoldi, F., Latib, A., Cosgrave, J., Montorfano, M., Carlino, M., Sangiorgi, G.M., Castelli, A., Godino, C., Magni, V., Aranzulla, T.C., Romagnoli, E. & Colombo, A. 2008, "Dual antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients taking chronic oral anticoagulation", *JACC. Cardiovascular interventions,* vol. 1, no. 1, pp. 56-61.

Rogers, M.A., Blumberg, N., Saint, S., Langa, K.M. & Nallamothu, B.K. 2009, "Hospital variation in transfusion and infection after cardiac surgery: a cohort study", *BMC medicine,* vol. 7, pp. 37-7015-7-37.

Romagnoli E, Burzotta F, Trani C, Siviglia M, Biondi-Zoccai GG, Niccoli G, Leone AM, Porto I, Mazzari MA, Mongiardo R, Rebuzzi AG, Schiavoni G, Crea F. 2009, "EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention." *Heart,* vol. 95, no. 1, pp. 43-8.

Rossini, R., Musumeci, G., Lettieri, C., Molfese, M., Mihalcsik, L., Mantovani, P., Sirbu, V., Bass, T.A., Della Rovere, F., Gavazzi, A. & Angiolillo, D.J. 2008, "Long-Term Outcomes in Patients Undergoing Coronary Stenting on Dual Oral Antiplatelet Treatment Requiring Oral Anticoagulant Therapy", *The American Journal of Cardiology,* vol. 102, no. 12, pp. 1618-1623.

Rubboli, A., Sciahbasi, A., Briguori, C., Saia, F., Palmieri, C., Moroni, L.A., Calabro, P., Leone, A.M., Franco, N., Valgimigli, M., Varani, E., Santi, M., Pasqualini, P., Capecchi, A., Piccalo, G., Margheri, M., di Pasquale, G., Galvani, M., Bolognese, L., Gonzini, L., Maggioni, A.P. & WARfarin and coronary STENTing registry 2013, "In-hospital management and outcome of patients on warfarin undergoing coronary stent implantation: results of the multicenter, prospective WARfarin and coronary STENTing (WAR-STENT) registry", *The Journal of invasive cardiology,* vol. 25, no. 4, pp. 170-176.

Rubboli A., Colletta, M, Valencia J, Capecchi A, Franco N, Zanolla L, Vecchia LL, Piovaccari G, Di Pasquale G & for the WARfarin and Coronary STENTing (WAR-STENT) Study Group 2009, "Periprocedural Management and In-Hospital Outcome of Patients with Indication for Oral Anticoagulation Undergoing Coronary Artery Stenting", *Journal of interventional cardiology,* vol. 22, no. 4, pp. 390-397.

Rudersdorf, P.D., Abolhoda, A., Carey, J.S., Danielsen, B. & Milliken, J.C. 2013, "Adverse Events After Coronary Revascularization Procedures in California 2000 to 2010", *The American Journal of Cardiology,* vol. 112, no. 4, pp. 483-487.

Ruiz-Nodar, J.M., Marín, F., Sánchez-Payá, J., Hurtado, J.A., Valencia-Martín, J., Manzano-Fernández, S., Roldán, V., Pérez-Andreu, V., Sogorb, F., Valdés, M. & Lip, G.Y.H. 2009, "Efficacy and safety of drug-eluting stent use in patients with atrial fibrillation", *European heart journal,* vol. 30, no. 8, pp. 932-939.

Rumsfeld JS, MaWhinney S, McCarthy M Jr, Shroyer AL, VillaNueva CB, O'Brien M, Moritz TE, Henderson WG, Grover FL, Sethi GK, Hammermeister KE. 1999, "Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. Participants of the Department of Veterans Affairs Cooperative Study Group on Processes, Structures, and Outcomes of Care in Cardiac Surgery." *JAMA*, vol. 281, no. 14, pp. 1298-303.

Salonen, JT, Tuomilehti J, Nissinen A, Kaplan GA & Puska P. 1989, "Contribution of Risk Factor Changes to the Decline in Coronary Incidence During the North Karelia Project: A Within-Community Analysis", *International journal of epidemiology,* vol. 18, no. 3, pp. 595-601.

Santangeli, P., Di Biase, L., Themistoclakis, S., Raviele, A., Schweikert, R.A., Lakkireddy, D., Mohanty, P., Bai, R., Mohanty, S., Pump, A., Beheiry, S., Hongo, R., Sanchez, J.E., Gallinghouse, G.J., Horton, R., Dello Russo, A., Casella, M., Fassini, G., Elayi, C.S., Burkhardt, J.D., Tondo, C. & Natale, A. 2013, "Catheter ablation of atrial fibrillation in hypertrophic cardiomyopathy: long-term outcomes and mechanisms of arrhythmia recurrence", *Circulation.Arrhythmia and electrophysiology,* vol. 6, no. 6, pp. 1089-1094.

Santarpino, G., Pfeiffer, S., Vogt, F., Hinzmann, M., Concistre, G. & Fischlein, T. 2013, "Advanced age per se should not be an exclusion criterion for minimally invasive aortic valve replacement", *The Journal of heart valve disease,* vol. 22, no. 4, pp. 455-459.

Schachner T, Zimmer A, Nagele G, Laufer G, Bonatti J. 2005 "Risk factors for late stroke after coronary artery bypass grafting." *The Journal of thoracic and cardiovascular surgery*, vol. 130, no. 2, pp. 485-90.

Schatz RA, Baim DS, Leon M, Ellis SG, Goldberg S, Hirshfeld JW, Cleman MW, Cabin HS, Walker C, Stagg J, et al. 1991, "Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study." *Circulation* vol. 83, no. 1, pp. 148-61.

Schmidt, M., Jacobsen, J.B., Lash, T.L., Botker, H.E. & Sorensen, H.T. 2012, "25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study", *British Medical Journal (Clinical research ed.),* vol. 344, pp. e356.

Serruys, P.W., de Jaegere, P., Kiemeneij, F., Macaya, C., Rutsch, W., Heyndrickx, G., Emanuelsson, H., Marco, J., Legrand, V. & Materne, P. 1994, "A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group", *The New England journal of medicine,* vol. 331, no. 8, pp. 489-495.

Serruys, P.W., Morice, M., Kappetein, A.P., Colombo, A., Holmes, D.R., Mack, M.J., Ståhle, E., Feldman, T.E., van, d.B., Bass, E.J., Van Dyck, N., Leadley, K., Dawkins, K.D. & Mohr, F.W. 2009, "Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease", *New England Journal of Medicine,* vol. 360, no. 10, pp. 961-972.

Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. 2009, "The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery." *The Annals of Thoracic Surgery*, vol. 88(1 Suppl), pp. 2-22.

Sharma, A., Walker, L.G. & Monson, J.R. 2013, "Baseline quality of life factors predict long term survival after elective resection for colorectal cancer", *International journal of surgical oncology,* vol. 2013, pp. 269510.

Sharma, A.D., Slaughter, T.F., Clements, F.M., Sreeram, G., Newman, M.F., Phillips-Bute, B., Bredehoeft, S.J., Smith, P.K. & Stafford-Smith, M. 2002, "Association of leukocyte-depleted blood transfusions with infectious complications after cardiac surgery", *Surgical Infections,* vol. 3, no. 2, pp. 127-133.

Sin DD, Wu L, Man SF. 2005, "The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature." *Chest*, vol. 127, no. 14, pp. 1952–1959.

Sirola, J., Pitkälä, K.H., Tilvis, R.S., Miettinen, T.A. & Strandberg, T.E. 2011, "Definition of frailty in older men according to questionnaire data (RAND-36/SF-36): The Helsinki Businessmen Study", *The journal of nutrition, health & aging,* vol. 15, no. 9, pp. 783-787.

Sjöland, H., Wiklund, I., Caidahl, K., Hartford, M., Karlsson, T. & Herlitz, J. 1999, "Improvement in quality of life differs between women and men after coronary artery bypass surgery", *Journal of internal medicine,* vol. 245, no. 5, pp. 445-454.

Smith PK, Goodnough LT, Levy JH, Poston RS, Short MA, Weerakkody GJ, Lenarz LA. 2012, "Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis." *Journal of the American College of Cardiology*, vol. 60, no. 5, pp. 388-96.

Smolina, K., Wright, F.L., Rayner, M. & Goldacre, M.J. 2012, "Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study", *British Medical Journal (Clinical research ed.),* vol. 344, pp. d8059.

Sneader W. 2000, "The discovery of aspirin: a reappraisal." *British Medical Journal*, vol. 321, no.7276, pp.1591-4.

Snyder-Ramos, S.A., Möhnle, P., Weng, Y.-., Böttiger, B.W., Kulier, A., Levin, J. & Mangano, D.T. 2008, "The ongoing variability in blood transfusion practices in cardiac surgery", *Transfusion,* vol. 48, no. 7, pp. 1284-1299.

Soyombo, A.A., Angelini, G.D., Bryan, A.J. & Newby, A.C. 1993, "Surgical preparation induces injury and promotes smooth muscle cell proliferation in a culture of human saphenous vein", *Cardiovascular research,* vol. 27, no. 11, pp. 1961-1967.

Speiss, B.D. 2002, "Transfusion and outcome in heart surgery", *Annals of Thoracic Surgery,* vol. 74, no. 4, pp. 986-987.

Spencer, F.A., Moscucci, M., Granger, C.B., Gore, J.M., Goldberg, R.J., Steg, P.G., Goodman, S.G., Budaj, A., FitzGerald, G., Fox, K.A.A. & for the GRACE Investigators 2007, "Does Comorbidity Account for the Excess Mortality in Patients With Major Bleeding in Acute Myocardial Infarction?", *Circulation,* vol. 116, no. 24, pp. 2793-2801.

Steenkiste AR, Baim DS, Sipperly ME, Desvigne-Nickens P, Robertson T, Detre K. 1991, "The NACI Registry: an instrument for the evaluation of new approaches to coronary intervention. The NACI Investigators." *Catheterization and cardiovascular diagnosis*, vol. 23, no. 4, pp. 270-81.

Steg, P.G., Goldberg, R.J., Gore, J.M., Fox, K.A., Eagle, K.A., Flather, M.D., Sadiq, I., Kasper, R., Rushton-Mellor, S.K., Anderson, F.A. & GRACE Investigators 2002, "Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE)", *The American Journal of Cardiology,* vol. 90, no. 4, pp. 358-363.

Stover, E.P., Siegel, L.C., Parks, R., Levin, J., Body, S.C., Maddi, R., D'Ambra, M.N., Mangano, D.T. & Spiess, B.D. 1998, "Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: A 24-institution study", *Anesthesiology,* vol. 88, no. 2, pp. 327-333.

Sun JC, Whitlock R, Cheng J, Eikelboom JW, Thabane L, Crowther MA, Teoh KH. 2008, "The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies." *European Heart Journal*, vol. 29, no. 8, pp. 1057-71.

Sündermann SH, Dademasch A, Seifert B, Rodriguez Cetina Biefer H, Emmert MY, Walther T, Jacobs S, Mohr FW, Falk V, Starck CT. 2014, "Frailty is a predictor of short- and mid-term mortality after elective cardiac surgery independently of age." *Interactive Cardiovascular and Thoracic Surgery*, vol. 18, no. 5, pp. 580-5.

Surgenor, S.D., Kramer, R.S., Olmstead, E.M., Ross, C.S., Sellke, F.W., Likosky, D.S., Marrin, C.A.S., Helm Jr., R.E., Leavitt, B.J., Morton, J.R., Charlesworth, D.C., Clough, R.A., Hernandez, F., Frumiento, C., Benak, A., DioData, C. & O'Connor, G.T. 2009, "The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery", *Anesthesia and Analgesia,* vol. 108, no. 6, pp. 1741-1746.

Swenson J., Clinch J.J. 2000, "Assessment of quality of life in patients with cardiac disease: the role of psychosomatic medicine." *J Psychosomatic Research*, vol. 48, no. 4-5,pp. 405-415.

Székely, A., Nussmeier, N.A., Miao, Y., Huang, K., Levin, J., Feierfeil, H. & Mangano, D.T. 2011, "A multinational study of the influence of health-related quality of life on in-hospital outcome after coronary artery bypass graft surgery", *American Heart Journal,* vol. 161, no. 6, pp. 1179-1185.e2.

Taggart, D.P., D'Amico, R. & Altman, D.G. 2001a, "Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries", *Lancet,* vol. 358, no. 9285, pp. 870-875.

Taggart, D.P. & Westaby, S. 2001b, "Neurological and cognitive disorders after coronary artery bypass grafting", *Current opinion in cardiology,* vol. 16, no. 5, pp. 271-276.

Takaro, T., Hultgren, H.N., Lipton, M.J. & Detre, K.M. 1976, "The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions", *Circulation,* vol. 54, no. 6 Suppl, pp. III107-17.

Tanaka, S., Sakata, R., Marui, A., Furukawa, Y., Kita, T., Kimura, T. & CREDO-Kyoto Investigators 2012, "Predicting long-term mortality after first coronary revascularization: - the Kyoto model -", *Circulation journal : official journal of the Japanese Circulation Society,* vol. 76, no. 2, pp. 328-334.

Tang XF, Fan JY, Meng J, Jin C, Yuan JQ, Yang YJ. 2014, "Impact of new oral or intravenous P2Y12 inhibitors and clopidogrel on major ischemic and bleeding events in patients with coronary artery disease: A meta-analysis of randomized trials." *Atherosclerosis*, 2014 Apr;233(2):568-578.

Tanguay JF, Bell AD, Ackman ML, Bauer RD, Cartier R, Chan WS, Douketis J, Roussin A, Schnell G, Verma S, Wong G, Mehta SR; Canadian Cardiovascular Society. 2013, "Focused 2012 update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy." *Canadian Journal of Cardiology*, vol. 29, no. 11, pp. 1334-45.

Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg, P.G., James, S.K., Atar, D., Badano, L.P., Blomstrom-Lundqvist, C., Borger, M.A., Di Mario, C., Dickstein, K., Ducrocq, G., Fernandez-Aviles, F., Gershlick, A.H., Giannuzzi, P., Halvorsen, S., Huber, K., Juni, P., Kastrati, A., Knuuti, J., Lenzen, M.J., Mahaffey, K.W., Valgimigli, M., van 't Hof, A., Widimsky, P. & Zahger, D. 2012, "ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation", *European heart journal,* vol. 33, no. 20, pp. 2569-2619.

Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Kolh P, Wijns W, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. 2010, "Guidelines on myocardial revascularization." *European Journal of Cardiothoracic Surgery*.vol. 38, Suppl:S1-S52.

Teo, K.K., Sedlis, S.P., Boden, W.E., O'Rourke, R.A., Maron, D.J., Hartigan, P.M., Dada, M., Gupta, V., Spertus, J.A., Kostuk, W.J., Berman, D.S., Shaw, L.J., Chaitman, B.R., Mancini, G.B.J. & Weintraub, W.S. 2009, "Optimal Medical Therapy With or Without Percutaneous Coronary Intervention in Older Patients With Stable Coronary Disease: A Pre-Specified Subset Analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) Trial", *Journal of the American College of Cardiology,* vol. 54, no. 14, pp. 1303-1308.

ter Horst, R., Markou, A.L.P. & Noyez, L. 2012, "Prognostic value of preoperative quality of life on mortality after isolated elective myocardial revascularization", *Interactive CardioVascular and Thoracic Surgery,* vol. 15, no. 4, pp. 651-654.

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD; Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA; ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H; Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ; Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW; Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J; Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML; Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G; Trials & Registries Subcommittee, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D; Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines(CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. 2012, "Third universal definition of myocardial infarction." *Journal of the American College of Cardiology*, vol. 60, no. 16, pp. 1581-98.

Toth, G., De Bruyne, B., Casselman, F., De Vroey, F., Pyxaras, S., Di Serafino, L., Van Praet, F., Van Mieghem, C., Stockman, B., Wijns, W., Degrieck, I. & Barbato, E. 2013, "Fractional Flow Reserve–Guided Versus Angiography-Guided Coronary Artery Bypass Graft Surgery", *Circulation,* vol. 128, no. 13, pp. 1405-1411.

Toumpoulis, I.K., Anagnostopoulos, C.E., Balaram, S.K., Rokkas, C.K., Swistel, D.G., Ashton Jr, R.C. & DeRose Jr, J.J. 2006, "Assessment of independent predictors for long-term mortality between women and men after coronary artery bypass grafting: Are women different from men?", *The Journal of thoracic and cardiovascular surgery,* vol. 131, no. 2, pp. 343-351.

Toumpoulis, I.K., Anagnostopoulos, C.E., DeRose, J.J. & Swistel, D.G. 2004, "European system for cardiac operative risk evaluation predicts long-term survival in patients with coronary artery bypass grafting", *European Journal of Cardio-Thoracic Surgery,* vol. 25, no. 1, pp. 51-58.

Turrentine, F.E., Wang, H., Simpson, V.B. & Jones, R.S. 2006, "Surgical Risk Factors, Morbidity, and Mortality in Elderly Patients", *Journal of the American College of Surgeons,* vol. 203, no. 6, pp. 865-877.

Unger, F., Serruys, P.W., Yacoub, M.H., Ilsley, C., Paulsen, P.K., Nielsen, T.T., Eysmann, L. & Kiemeneij, F. 2003, "Revascularization in multivessel disease: Comparison between two-year outcomes of coronary bypass surgery and stenting", *Journal of Thoracic and Cardiovascular Surgery,* vol. 125, no. 4, pp. 809-820.

Vainiola, T., Roine, R.P., Suojaranta-Ylinen, R., Vento, A. & Sintonen, H. 2013, "Can factors related to mortality be used to predict the follow-up health-related quality of life (HRQoL) in cardiac surgery patients?", *Intensive and Critical Care Nursing,* vol. 29, no. 6, pp. 337-343.

Valgimigli, M., Tebaldi, M., Borghesi, M., Vranckx, P., Campo, G., Tumscitz, C., Cangiano, E., Minarelli, M., Scalone, A., Cavazza, C., Marchesini, J. & Parrinello, G. 2014, "Two-Year Outcomes After First- or Second-Generation Drug-Eluting or Bare-Metal Stent Implantation in All-Comer Patients Undergoing Percutaneous Coronary Intervention: A Pre-Specified Analysis From the PRODIGY Study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY)", *JACC: Cardiovascular Interventions,* vol. 7, no. 1, pp. 20-28.

van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briët E. 1993, "Bleeding complications in oral anticoagulant therapy. An analysis of risk factors." *Archives of Internal Medicine*, vol.153,no.13, pp.1557-62

Van Straten, A.H.M., Bekker, M.W.A., Soliman Hamad, M.A., Van Zundert, A.A.J., Martens, E.J., Schönberger, J.P.A.M. & De Wolf, A.M. 2010, "Transfusion of red blood cells: The impact on short-term and long-term survival after coronary artery bypass grafting, a ten-year follow-up", *Interactive Cardiovascular and Thoracic Surgery,* vol. 10, no. 1, pp. 37-42.

Van Straten, A.H.M., Soliman Hamad, M.A., Van Zundert, A.J., Martens, E.J., Schönberger, J.P.A.M. & De Wolf, A.M. 2009, "Preoperative hemoglobin level as a predictor of survival after coronary artery bypass grafting: A comparison with the matched general population", *Circulation,* vol. 120, no. 2, pp. 118-125.

Vartiainen, E., Jousilahti, P., Alfthan, G., Sundvall, J., Pietinen, P. & Puska, P. 2000, "Cardiovascular risk factor changes in Finland, 1972–1997", *International journal of epidemiology,* vol. 29, no. 1, pp. 49-56.

Vartiainen, E., Laatikainen, T., Peltonen, M., Juolevi, A., Männistö, S., Sundvall, J., Jousilahti, P., Salomaa, V., Valsta, L. & Puska, P. 2010, "Thirty-five-year trends in cardiovascular risk factors in Finland", *International journal of epidemiology,* vol. 39, no. 2, pp. 504-518.

Vasques, F., Rainio, A., Heikkinen, J., Mikkola, R., Lahtinen, J., Kettunen, U., Juvonen, T. & Biancari, F. 2013, "Off-pump versus on-pump coronary artery bypass surgery in patients aged 80 years and older: institutional results and meta-analysis", *Heart and vessels,* vol. 28, no. 1, pp. 46-56.

Villareal, R.P., Hariharan, R., Liu, B.C., Kar, B., Lee, V., Elayda, M., Lopez, J.A., Rasekh, A., Wilson, J.M. & Massumi, A. 2004, "Postoperative atrial fibrillation and mortality after coronary artery bypass surgery", *Journal of the American College of Cardiology,* vol. 43, no. 5, pp. 742-748.

Vineberg, A.M., 1949 "Development of anastomosis between the coronary vessels and a transplanted internal mammary artery." *Journal of Thoracic surgery*. vol. 18, no. 6, pp. 839-50

Wang, T.Y., Robinson, L.A., Ou, F., Roe, M.T., Ohman, E.M., Gibler, W.B., Smith Jr, S.C., Peterson, E.D. & Becker, R.C. 2008, "Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: Physician practice in the CRUSADE registry", *American Heart Journal,* vol. 155, no. 2, pp. 361-368.

Weintraub, W.S., Grau-Sepulveda, M., Weiss, J.M., O'Brien, S.M., Peterson, E.D., Kolm, P., Zhang, Z., Klein, L.W., Shaw, R.E., McKay, C., Ritzenthaler, L.L., Popma, J.J., Messenger, J.C., Shahian, D.M., Grover, F.L., Mayer, J.E., Shewan, C.M., Garratt, K.N., Moussa, I.D., Dangas, G.D. & Edwards, F.H. 2012, "Comparative Effectiveness of Revascularization Strategies", *New England Journal of Medicine,* vol. 366, no. 16, pp. 1467-1476.

Wu, C., Camacho, F.T., Wechsler, A.S., Lahey, S., Culliford, A.T., Jordan, D., Gold, J.P., Higgins, R.S.D., Smith, C.R. & Hannan, E.L. 2012, "Risk Score for Predicting Long-Term Mortality After Coronary Artery Bypass Graft Surgery", *Circulation,* vol. 125, no. 20, pp. 2423-2430.

Yoo, J.S., Kim, J.B., Jung, S., Choo, S.J., Chung, C.H. & Lee, J.W. 2013, "Coronary artery bypass grafting in patients with left ventricular dysfunction: Predictors of long-term survival and impact of surgical strategies", *International journal of cardiology,* vol. 168, no. 6, pp. 5316-5322.

Yoon, Y., Kim, Y., Kim, S., Lee, J., Park, D., Kang, S., Lee, S., Lee, C.W., Park, S. & Park, S. 2013, "Impact of in-hospital bleeding according to the bleeding academic research consortium classification on the long-term adverse outcomes in patients undergoing percutaneous coronary intervention", *Catheterization and Cardiovascular Interventions,* [epub ahead of print]

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J. & Lisheng, L. 2004, "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study", *The Lancet,* vol. 364, no. 9438, pp. 937-952.

Zacharias, A., Habib, R.H., Schwann, T.A., Riordan, C.J., Durham, S.J. & Shah, A. 2004, "Improved survival with radial artery versus vein conduits in coronary bypass surgery with left internal thoracic artery to left anterior descending artery grafting", *Circulation,* vol. 109, no. 12, pp. 1489-1496.

Zhao M, Stampf S, Valina C, Kienzle RP, Ferenc M, Gick M, Essang E, Nührenberg T, Büttner HJ, Schumacher M, Neumann FJ. 2013, "Role of euroSCORE II in predicting long-term outcome after percutaneous catheter intervention for coronary triple vessel disease or left main stenosis." *International Journal of Cardiology*, vol. 168, no. 4, pp. 3273-9.