Impact of chronic total occlusions, arterial access site, and pretreatment with antiplatelet drugs on mortality in patients with ischemic heart disease:

A report from the SWEDEHEART registry

Christian Dworeck

Department of Molecular and Clinical Medicine

Institute of Medicine

Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

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Christian.Dworeck@vgregion.se

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ABSTRACT

Background

The treatment of ischemic heart disease has advanced substantially in the past half-century. However, despite these achievements, the survival rates in high-income countries such as Sweden have reached a plateau in the last decade. Strategies to further reduce mortality are needed.

Aims

To evaluate the impact of chronic total occlusions, the choice of arterial access site, and pretreatment with $P2Y_{12}$ inhibitors on mortality in patients with coronary artery disease.

Methods

This thesis is based on observational studies. We used data from the Swedish Web-system for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry and the Swedish National Cause of Death Register. All coronary procedures, angiographies and percutaneous coronary interventions (PCIs) performed in Sweden are registered in the SWEDEHEART registry. We used multiple imputation to impute missing data (Papers I–IV), propensity score (PS)

matching to adjust for known confounders (Papers II, IV), multilevel models to account for a hierarchical database (Paper II, III, IV), and instrumental variable analysis to adjust for known and unknown confounders (Paper III).

Results

In Paper I, we found an adjusted hazard ratio (HR) of 1.29 for death in patients with a chronic total occlusion (CTO), as compared to patients with coronary artery disease without a CTO. In Paper 2, pretreatment was not associated with better 30-day survival or differences in bleeding in STEMI patients. In Paper 3, pretreatment in NSTE-ACS patients was not associated with better 30-day survival but with a higher risk of in-hospital bleeding. In Paper IV, we could show that radial access (RA) in patients undergoing primary PCI for STEMI was associated with a lower risk of death (adjusted odds ratio (OR) 0.70) within 30 days, as compared to femoral access (FA).

Conclusion

The CTOs of coronary arteries are associated with increased mortality. Pretreatment with $P2Y_{12}$ receptor antagonists is not associated with reduced mortality in patients with acute coronary syndrome, but is associated with increased in-hospital bleeding in NSTE-ACS patients. Our findings in Paper II and III add external validity to the findings of randomized trials on the lack of benefits and potential harms of pretreatment. The use of radial artery access for primary PCI in STEMI is associated with reduced mortality in comparison to using FA. The findings in Paper IV support the ESC guideline recommendation for the use of RA in STEMI.

Keywords: Acute coronary syndrome, acute myocardial infarction, coronary artery disease, mortality, chronic total occlusion, pretreatment, antiplatelet, $P2Y_{12}$, radial access, PCI, SWEDEHEART, SCAAR, RIKS-HIA, cardiology

SAMMANFATTNING PÅ SVENSKA

Den här avhandlingen undersöker faktorer som påverkar dödlighet i kranskärlsjukdom. Kranskärlsjukdom orsakar cirka 15% av alla dödsfall i Sverige, och är därmed den vanligaste dödsorsaken för vuxna i Sverige. Både stabil och instabil kranskärlsjukdom orsakar dödsfall, men risken för den enskilda patienten är mycket högre när kranskärlssjukdom blir instabil och ett akut koronart syndrom – med ST-höjning på EKG (STEMI) eller utan (NSTE-ACS) - inträffar. Genom att använda våra unika och nästan heltäckande nationella register har vi kunnat göra studier som var och en är bland de största registerstudierna som gjorts.

Avhandlingen består av fyra delarbeten. I alla delarbeten har vi använt oss av data från svenska SWEDEHEART registret där nästan alla patienter som genomgår kranskärlsröntgen, PCI (delregister SCAAR) eller vårdas på hjärtintensiven (delregister RIKS-HIA) registreras.

I **delarbete 1** har vi undersökt om patienter som har en långvarig avstängning av ett kranskärl (chronic total occlusion, CTO) har en högre risk att dö jamfört med patienter som har en kranskärlssjukdom utan CTO. Detta arbete, som publicerades 2016, är en av världens största studier med denna frågeställning. Vi har undersökt betydelsen av CTO både för patienter med stabil och instabil kranskärlsjukdom, något som tidigare studier inte gjort. Vi kunde visa att patienter som har en CTO har en högre risk att dö än patienter utan CTO.

Delarbete 2 och 3 analyserar om patienter med akut koronart syndrom (instabil angina och hjärtinfarkt) har värde av att börja behandling med $P2Y_{12}$ receptor-antagonister (en grupp av läkemedel som är blodförtunnande genom att hämma blodplättarnas funktion) redan innan kranskärlsröntgen är gjord, en strategi som används i stora delar av världen och kallas för ”förbehandling”. I delarbete 2 visar vi att förbehandling inte är associerat med minskat dödlighet för patienter med STEMI men att förbehandlingen vid STEMI inte heller ökar blödningsrisken, som är en av de allvarligaste biverkningar av $P2Y_{12}$ receptor antagonister. I delarbete 3 kom vi fram till att förbehandling inte heller hos patienter med NSTE-ACS minskar dödligheten, men däremot ökar risken för dessa patienter att drabbas av blödning.

I **delarbete 4** har vi utvärderat om kranskärlsingrepp (PCI) vid STEMI är associerat med bättre chans att överleva om PCI görs via handledsartären, jämfört men det klassiska sättet att använda artären i ljumsken. Genom att analysera data från över 40.000 patienter kunde vi visa att ingrepp som utförs via handledens artär är

associerat med bättre överlevnad och mindre blödning jämfört med ingrepp som utförs via artären i ljumsken.

Slutsatsen från mina delarbeten är (i) att CTO är en viktig riskfaktor; (ii) att förbehandling, som är rutinbehandlingen vid både STEMI och NSTE-ACS på många ställen i Sverige och i världen, inte är associerat med bättre överlevnad varken för för patienter med STEMI eller NSTE-ACS, utan istället ökar risken för patienter med NSTE-ACS att drabbas av blödningskomplikationer; och (iii) att PCI via handledsartären istället för ljumskartären vid akut hjärtinfarkt är associerat med minskad dödlighet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Råmunddal T, Hoebers LP, Henriques JP, Dworeck C, Angerås O, Odenstedt J, Ioanes D, Olivecrona G, Harnek J, Jensen U, Aasa M, Albertsson P, Wedel H, Omerovic E

Prognostic Impact of Chronic Total Occlusions: A Report From SCAAR (Swedish Coronary Angiography and Angioplasty Registry)

JACC Cardiovasc Interv. 2016;9:1535-44

II. Redfors B, Dworeck C, Haraldsson I, Angerås O, Odenstedt J, Ioanes D, Petursson P, Völz S, Albertsson P, Råmunddal T, Persson J, Koul S, Erlinge D, Omerovic E

Pretreatment with $P2Y_{12}$ Receptor Antagonists in ST-Elevation Myocardial Infarction: A Report from the Swedish Coronary Angiography and Angioplasty Registry

European Heart Journal (2019) Apr 14; 40 (15):1202-1210

III. Dworeck C, Redfors B, Haraldsson I, Angerås O, Odenstedt J, Ioanes D, Petursson P, Völz S, Albertsson P, Råmunddal T, Persson J, Koul S, Erlinge D, Omerovic E

Pretreatment with $P2Y_{12}$ receptor antagonists in non-ST-Segment-Elevation Acute Coronary Syndromes: A report from the Swedish Coronary Angiography and Angioplasty Registry
Manuscript

IV. Dworeck C, Redfors B, Völz S, Haraldsson I, Angerås O, Råmunddal T, Ioanes D, Myredal A, Odenstedt J, Hirlekar G, Koul S, Fröbert O, Linder R, Venetsanos D, Hofmann R, Ulvenstam A, Petursson P, Sarno G, James S, Erlinge D, Omerovic E

Radial Artery Accesses is Associated with Lower Mortality in Patients Undergoing Primary PCI: A Report from the SWEDEHEART registry

Submitted

Contents

Abbreviations

ADP	Adenosine Diphosphate
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CI	Confidence Interval
CS	Cardiogenic Shock
DAPT	Dual Antiplatelet Therapy
DES	Drug-eluting Stent
ESC	European Society of Cardiology
FA	Femoral Access
FDA	U.S. Food and Drug Administration
HR	Hazard Ratio
IRA	Infarct-related Artery
IV	Instrument Variable
LAD	Left Anterior Descending Artery
LMWH	Low Molecular Weight Heparin
LVEF	Left Ventricular Ejection Fraction
LVEDV	Left Ventricular End Diastolic Volume
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
Non-STE-ACS	Non-ST-Elevation Acute Coronary Syndrome
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PPV	Positive Predictive Value

PS	Propensity Score
RA	Radial Access
RCT	Randomized Controlled Trial
SAQ	Seattle Angina Questionaire
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
ST	Stent Thrombosis
STEMI	ST-Elevation Myocardial Infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularisation

Introduction

This thesis is about observational studies in interventional cardiology. The four presented papers analyze data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), data from patients who underwent coronary angiography or percutaneous coronary intervention (PCI) in Sweden, and data from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA registry). Both registries are part of the Swedish Web-system for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.

The treatment of symptomatic ischemic heart disease (i.e., stable angina and acute coronary syndrome) has advanced substantially in the past half-century. However, despite these achievements, the survival rates in high-income countries such as Sweden have reached a plateau in the last decade. Cardiovascular disease continues to be the most common cause of death in these countries[1] and in Sweden, ischemic heart disease accounts for 43% of all cardiovascular deaths[2].

Several significant developments have occurred in the last decade. New potent antithrombotic drugs have been developed and are routinely used today in patients with acute coronary syndromes[3]. Recent advances in medical devices (e.g., stents, guidewires, catheters) and interventional techniques have created a much-needed methodological prerequisite for the successful treatment of chronic total occlusions (CTOs) in coronary arteries using PCI rather than coronary bypass surgery or pharmacological agents[4, 5]. These same developments have made it possible to use the radial artery rather than the femoral artery as the standard access for coronary interventions[6].

Before patients with CTOs are treated with PCI on a routine basis—a treatment strategy that is more technically demanding and more expensive, and associated with more severe complications—we need to evaluate whether the presence of a CTO on a diagnostic coronary angiography is associated with altered life expectancy in patients with ischemic heart disease (**Paper I**), as well as whether the successful treatment of a CTO with PCI improves symptoms or reduces mortality.

The development of potent oral antiplatelet agents-$P2Y_{12}$ receptor antagonists has been a significant breakthrough in the treatment of patients with acute coronary syndrome[3]. The first $P2Y_{12}$ antagonist that was used in humans in addition to

acetylsalicylic acid (ASA)—ticlopidine—has effectively reduced the risk of stent thrombosis (ST) after PCI[7, 8]. The implementation of dual antiplatelet therapy (ASA + $P2Y_{12}$ antagonists) has been an essential prerequisite for successful progress in stent technology ever since the 1990s. There are several clinically essential questions and concerns that have not been sufficiently addressed to date regarding treatment with $P2Y_{12}$ antagonists. One such concern is the optimal timing for the initiation of therapy with $P2Y_{12}$ antagonists in relation to the start of a PCI procedure. No trial has shown unequivocal evidence of benefits for pretreatment with the $P2Y_{12}$ antagonist (i.e., when the therapy is initiated before angiography). Nevertheless, the European and American guidelines recommend pretreatment with a $P2Y_{12}$ antagonist [9-11]. In **Paper II** and **Paper III,** we evaluate the association between pretreatment with the $P2Y_{12}$ antagonist and the relevant clinical outcomes in patients with acute coronary syndrome.

In **Paper IV**, we evaluate the association between the arterial access site (radial artery versus femoral artery) and the short-term prognosis in patients with ST-elevation myocardial infarction (STEMI) treated with PCI.

CTO

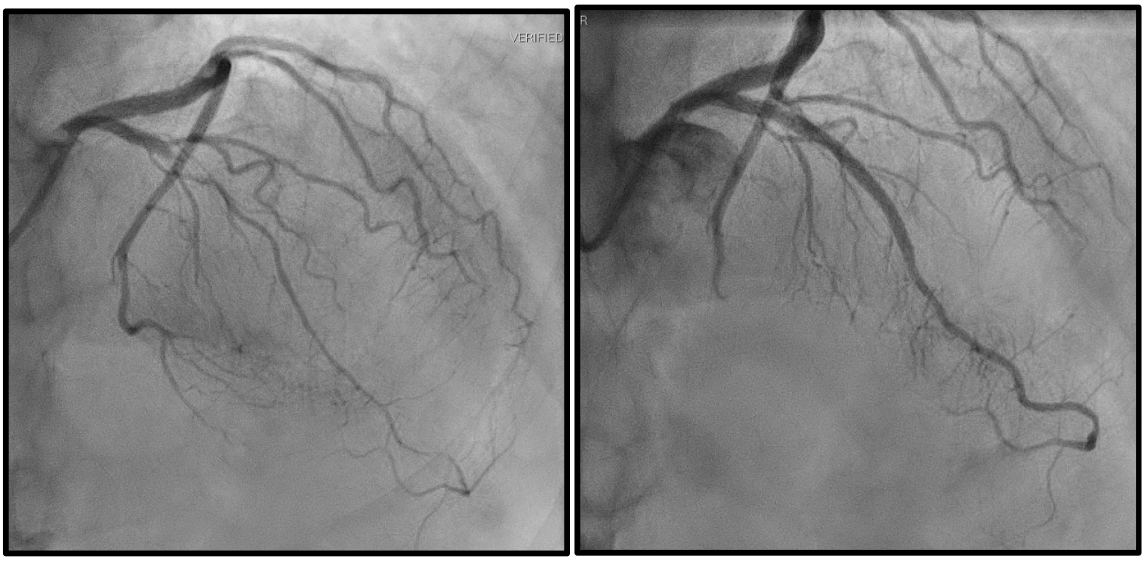

Figure 1: CTO in the LAD before PCI (left), LAD after PCI (right)

Recent advances in medical devices (e.g., stents, guidewires, catheters) and interventional techniques have created a much-needed methodological prerequisite for the successful treatment of CTOs in coronary arteries using PCI rather than coronary bypass surgery or pharmacological agents.

The CTO of a coronary artery is **defined** as a complete blockage of the vessel, i.e., the absence of antegrade flow (Thrombolysis in Myocardial Infarction (TIMI), grade 0 flow) in the occlusion, of a known or estimated duration of at least three months.[12] [13]

The **prevalence** of CTO in the main population is not known. The largest study on CTO prevalence in patients undergoing coronary angiography (CABG operated patients excluded), published by our team in 2014[14], found that 11.5% of patients angiographied for all indications in Sweden had a CTO, and 16% of all patients with the diagnosis of coronary artery disease after coronary angiography. Comparable results showing a CTO in 13.3% of all patients angiographied (CABG excluded) were found in 2015 in Italy[15] and in 2012 in Canada[16], where 14.7% of all 14,439 patients angiographied and 18.4% of all patients angiographied with a diagnosis of CAD had a CTO, respectively. A German study[17] conducted in 2012 used stable angina as the denominator and found a CTO in 33% of 2002 patients. In the cohort of CABG-operated patients, the prevalence of CTO was much higher (54% in the Canadian registry[16], 52% in the Italian[15] registry), and lower in patients who

presented with STEMI (8.6% CTO in a non-IRA in HORIZON-AMI[18], 10% in the Canadian registry[16], 13% in the Netherlands[19]).

We knew little about the **prognostic impact** of a CTO. Earlier studies had shown that a CTO in a non-infarction-related artery imposes a higher risk of short- and long-term mortality in patients treated for STEMI[18, 19]. Before the study presented as Paper I of this thesis was conducted, no study had investigated the prognostic impact in patients with stable angina.

In about 90% of patients with a CTO, collaterals can be detected by angiography[5]. Nevertheless, even myocardium supplied by well-developed collaterals is found to be ischemic on exercise[5, 20], i.e., the viable myocardium distal of a CTO is ischemic, regardless of the magnitude of collateral perfusion[21, 22].

Data on the **benefit** of CTO-PCI is scarce[4]: To date, there are only three published **RCTs** on this matter. The EXPLORE trial[23] randomized 304 patients treated for STEMI who had a CTO in a non-IRA vessel to CTO-PCI within seven days versus medical treatment. The primary outcome measures—left ventricular ejection fraction and left ventricular end-diastolic volume on the cardiac MRI after four months—or major adverse cardiac events (MACE) were not different in the two groups.

In one of the subgroup analyses in EXPLORE, the CTO location had a $p < 0.02$ as a benefit of PCI in patients with a CTO in the left anterior descending artery (LAD). No significant difference in MACE was found, but the differnce in cardiac death nearly reached significance ($p = 0{,}056$). The **EURO-CTO** trial[24] was preliminarily terminated after the enrollment of 396 patients instead of 1,200 patients as planned. In this study, non-CTO lesions were treated before randomization. The study found improvement in the primary endpoint change in health status as assessed with the Seattle Angina Questionaire for patients treated with PCI compared to medical treatment, but no difference in MACE. Another RCT, **DECISION-CTO**, which randomized 834 patients to PCI or medical treatment, was halted in 2016 due to slow enrollment and has been presented as a negative trial[25], but has not been published so far[26]. Recently, a small trial[27] randomized 65 patients with a CTO in the right coronary artery to CTO-PCI versus medical treatment and demonstrated a greater decrease in the ischemic burden on the stress MRI in PCI patients.

Several **observational** studies have compared the **benefit of successful versus unsuccessful** CTO-PCI[4]. In the OPEN-CTO registry, patients with successful CTO-PCI had a better rating on the Seattle Angina Questionaire Quality of Life Index compared to patients for whom PCI was unsuccessful. Jones et al.[28] reported an improved five-year survival rate after successful versus unsuccessful CTO-PCI. A

metaanalysis[29] performed in 2015 on 25 observational studies found less residual angina, less of a need for subsequent CABG, a lower risk for MACE, and lower mortality in patients after successful versus unsuccessful CTO-PCI. A 2012 metaanalysis[30] of 13 studies, again comparing successful to unsuccessful CTO-PCI, found a reduction in angina status, mortality, and the need for CABG.

Other observational studies have compared the **benefit of CTO-PCI versus medical therapy**[4, 26] and some reported improved angina status[15] and a lower rate of cardiac death and MACE after CTO-PCI[15], while other studies have reported no difference in mortality[31]. A study[32] comparing medical treatment versus the revascularisation (PCI, CABG) of well-collateralized CTO found a benefit in terms of MACE and mortality for revascularization.

Other published studies have reported positive effects on depression after a CTO-PCI[33] or found improvement in a six-minute walking test [34], peak oxygen consumption[35], and the aerobic threshold[36], though all of these studies were done with small numbers of patients and without a medically treated control group.

Procedural **success rates** have been improving over time: A 2013 metaanlysis[37] of 65 studies reported that pooled angiographic success rates improved from 68% in studies published from 2000 to 2002 to 79.4% in studies published from 2009 to 2011. Success rates are known to be dependent on center and operator volume[10, 38].

CTO-PCI is associated with higher rates of **complication** compared to non-CTO PCI[4, 38]. CTO-PCI demands a greater contrast volume and more radiation[38]. The overall complication rate reported between 2012 and 2017 varies by approximately 3%[4]. In a large British registry[39] of more than 500,000 PCIs, 1.4% of 25,558 CTO interventions and 0.3% of all PCIs had a coronary perforation, while in another current CTO registry[40], perforation occurred in 4.1% of 2,097 CTO-PCIs, with 0.6% requiring pericardiocentesis. Nevertheless**,** major complications with CTO-PCI have decreased over time: The 2013 metalalysis[37] cited above reported a major complication (death, emergency CABG, stroke) rate of 1.6% from 2000 to 2002 and of 0.5% from 2009 to 2011.

The treatment of a CTO is **indicated**, as all medical treatment is, when the anticipated benefit of the intervention outweighs the potential risks[4, 5, 10]. Before patients with CTOs are treated with PCI on a routine basis—a treatment strategy that is more technically demanding, more expensive, and associated with more severe complications—we need to further evaluate whether the presence of a CTO on a diagnostic coronary angiography, as well as whether success or failure in the treatment of CTO with PCI, is associated with altered life expectancy in patients

with ischemic heart disease. With the current data, CTO-PCI is indicated for symptom relief and the improvement of quality of life[4, 5]. The current ESC guideline[10] on myocardial revascularisation recommends (IIaB) that PCI of a CTO "should be considered in patients with angina resistant to medical therapy or with a large area of documented ischemia in the territory of the occluded vessel."

Pretreatment

Figure 2: Non-activated platelet (left) and activated platelet (right). (printed with permission from SciencePhotoLibrary)

In acute coronary syndromes, plaque rupture or erosion disrupts the endothelial layer of the atherosclerotic coronary artery and circulating platelets are suddenly exposed to collagen, von Willebrand factor, and other platelet-activating substances. The resulting platelet adhesion, platelet activation (with the change of shape and degranulation releasing ADP and thromboxane A2, which induces further platelet activation and expression of fibrinogen-binding GpIIb/IIIa receptors), and aggregation are fundamental parts of intracoronary thrombosis that, in acute coronary syndromes, partly or totally occludes the coronary vessel and causes ischemia, necrosis, heart failure, and death.[1 41, 42]

In Papers II and III of this thesis, we study whether the treatment of ACS patients with antiplatelet drugs of the $P2Y_{12}$ receptor antagonist type before coronary angiography is beneficial compared to treatment after coronary angiography.

Today, two different types of oral antiplatelet drugs are routinely used in ACS patients to treat thrombosis: $P2Y_{12}$ receptor antagonists and acetylsalicylic acid.

$P2Y_{12}$ receptor antagonists

$P2Y_{12}$ receptor antagonists, or ADP-receptor blockers, act on the $P2Y_{12}$ type of the platelet's ADP (adenosine diphosphate) receptor[43-45].

The first $P2Y_{12}$ –receptor antagonist was coincidentally developed in the 1970s, and although the prothrombotic effect of ADP has by this time already been known for some years, it took 30 more years until the $P2Y_{12}$ receptor was isolated as the target of this drug.

In 1960, A.J. Hellem observed at Rikshospitalet in Oslo that a small molecule originating from red blood cells caused platelets to adhere to glass[43]. The next year, researchers in Oslo identified this small molecule as the purine adenosine diphosphate (ADP), proved that it converts non-adhesive platelets into adhesive platelets and thus causes platelet aggregation, and assumed that ADP release based on cellular damage might play an important role in thrombosis.[46] ADP does not normally circulate in the bloodstream, but is stored in large quantities in platelets' dense granules, which can release ADP when they are stimulated by other substances, like collagen or thrombin[43, 47 48 41]. **ADP** causes platelets to change shape from disc-shaped to a spherical structure with pseudopods with a substantial increase in surface area[43] to increase cytosolic free calcium[43], to express a fibrinogen binding site (GP IIb/IIIa receptor) [47], and finally to aggregate to a white thrombus by adhering to each other with the help of fibrin links[49]. In 1964, it was determined that other purines, adenosine and adenosine triphosphate[50], are inhibitors of ADP-induced platelet aggregation[43, 49 51].

Ticlopidine and clopidogrel were developed when the exact site of action of these thienopyridines was still unknown and the first antagonist of the $P2Y_{12}$ receptor was created by chance[43 47]: In 1972, French scientists were searching for new anti-inflammatory drugs related to Tinoridine, a drug from the chemical class thienopyridine with anti-inflammatory properties that was published in 1970, and started synthesizing derivates and testing them on rats.[52] They did not succeed in finding anti-inflammatory agents, but some of the compounds showed unanticipated antiplatelet activity and the most active was selected for further

development and named ticlopidine[52]. In 1978, the thienopyridine ticlopidine hit the market in France under the name Ticlid, was tested in clinical trials (initially in stroke patients[53]), and reached the U.S. market in 1991. Soon after marketing, the drug showed severe side effects in some patients: agranulocytosis and pancytopenia. So, in France, the search for ticlopidine analogs with an improved benefit/risk ratio continued, and after testing thousands of analogs, **clopidogrel** was found. The preclinical development started in 1987 and led to the worldwide launch of clopidogrel in 1998, which became the second-bestselling drug in the first decade of the 21st century [52].

Today, we know that there are different types of purinergic receptors (P-receptors) on platelets (as on other cell surfaces)[54]. In 1995, a French-Italian team was able to show that there are at least two different P2-receptors for ADP on platelets, one inducing shape change and another coupled to the inhibition of adenylyl cyclase and causing platelet aggregation, with the latter being receptive to thienopyridines[47]. This receptor then had several names ($P2_T$ for thrombocyte, $P2Y_{AC}$ for adenylyl cyclase, $P2Y_{ADP}$) and was finally called the **$P2Y_{12}$ receptor** when it was cloned and analyzed in San Francisco in 2001[47, 55] and identified as the clopidogrel-receptor[56].

The scientists who developed the new antiplatelet drugs knew that clopidogrel, like ticlopidine, was a prodrug that had to be ingested orally to be processed in the liver by cytochrome P450 pathways to an active metabolite, but it was not until 2001, 30 years after the discovery of ticlopidine, that some of them succeeded in isolating the active metabolite.[52] Interestingly, the detection of ticlopidine as an active antiplatelet drug would not have been possible if the initial tests had not been performed on rats but instead on, e.g., guinea pigs, which lack the enzyme to produce the active metabolite[52].

It has been argued that clopidogrel's main drawbacks are based on its status as a prodrug: Because of the mandatory cytochrome P450-dependent[45] metabolism in the liver, the pharmacodynamic effect is delayed and varies substantially between individuals (15–40% of patients are poor responders)[45 57]. In addition, clopidogrel binds (like all thienopyridines[45]) irreversibly to the $P2Y_{12}$ receptor so that the effect lasts until new thrombocytes are ready to replace them. Because of these downsides of clopidogrel, the search for an ideal antiplatelet drug continued and led to the last-generation $P2Y_{12}$ antagonists prasugrel and ticagrelor.

Prasugrel, a third-generation thienopyridine, is a prodrug like the second-generation thienopyridine clopidogrel, but is less dependent on hepatic cytochrome P450 activity and therefore faster acting (maximal effect after approximately 30

minutes instead of 3–5 hours for clopidogrel) and shows less variation in the effect size[45, 57, 58]. The differences are in the pharmacokinetics; The active metabolites of clopidogrel and prasugrel are chemically similar and have the same potency[3, 57]. Prasugrel was tested in the TRITON TIMI-38 trial[59] (2007) against clopidogrel in invasively treated ACS patients following coronary angiography and the trial found higher efficiency but lower safety for prasugrel. The FDA later criticized the trial for shortcomings in design and disadvantages for patients treated with clopidogrel[60].

Ticagrelor is the first oral non-thienopyridine $P2Y_{12}$ antagonist, an ATP analog that belongs to the new chemical class of cyclopentyl-triazolopyrimidines[57 51]. It is a direct-acting drug (i.e., not a prodrug that requires conversion to an active metabolite) and a reversible $P2Y_{12}$ antagonist[57] that binds to a $P2Y_{12}$ binding site that differs from the adenosine binding site[51]. The PLATO trial[61], published in 2009, compared the use of ticagrelor and clopidogrel in ACS patients and reported better prevention of the composite endpoint death, MI, or stroke without differences in overall bleeding (but an increase in non-CABG bleeding).

ASA

The history of antiplatelet drugs began with Acetylsalicylic Acid (ASA). An essential step in platelet activation (initiated by platelet adhesion to collagen or von Willebrand factor) is platelets' synthesis and release of the prostaglandin Thromboxane A2 and ADP.

ASA irreversibly blocks platelets' cyclooxygenase by acetylation and thus reduces the production of the platelet-aggregation-stimulating Thromboxane A_2[1, 44] (Thromboxane was named after its platelet aggregation property at Karolinska Institute in the 1970s[62, 63]). Bark and leaves from the willow tree, *Salix* [64], were used as anti-inflammatory and painkilling drugs for more than 3,000 years[65] and recommended by Hippocrates 2,400 years ago[66] for use as analgetics in childbirth, and analgesia and anti-inflammation were even the indications for the drug Aspirin after the synthetic production of ASA (acetylated salicylate) in Germany at the turn of the 19th to the 20th century[66]. The initially extracted salicylate, named after the tree Salix, had severe gastric side effects, illustrated by the fact that its current indication is usage as a keratolytic for warts[66]. Before synthetic production, meadowsweet (spiraea ulmaria) was used for the production of ASA due to its higher concentration of salicylates, hence the name Aspirin was selected (**a**cetyl **spir**säure with the at-the-time popular suffix –**in**, as in Hero**in** by the same company Bayer or as in the U.S. Hepar**in**).[66]

The effect of ASA on platelet aggregation first became known in the 1960s[63, 65, 66] and the first major study with clinical cardiovascular endpoints was conducted in the late 1970s to prove ASA was effective in the secondary prevention of stroke [67] In 1983, a RCT showed a reduction of the rate of MI or death by 50% in patients with unstable angina treated with ASA, as compared to a placebo[68]. In 1984, a RCT proved ASA was effective in preventing early and late saphenous vein graft occlusion after CABG[69], while in 1985, a Canadian multicenter RCT confirmed a 51% risk reduction (cardiac death or MI) in unstable angina[70] and three years later, the ISIS-2 trial showed a significant improved survival rate (25 prevented deaths for every 1,000 patients taking one month of ASA) and fewer re-infarctions and strokes in STEMI patients taking ASA alone or initially in combination with streptokinase[71, 72].

A medicine used for thousands of years could half the risk of death and MI. Based on this fantastic data, **ASA** has from the 1990s to today been a **standard acute and secondary preventive treatment** for all subtypes of acute coronary syndromes.

Development of DAPT

In parallel, **PCI** was evolving. Andreas Gruentzig chose Aspirin as an antithrombotic treatment for balloonangioplasty[73], a medication later (in combination with Dipyridamole) deemed effective in preventing post-PCI (balloon angioplasty) infarction[74]. With **stent implantation** emerging in the 1990s, after the first human coronary stent implantation was done in France in 1986[75], life-threatening ST became a new clinical problem of extensive concern, occurring in the early series in up to one of four cases, despite heavy anticoagulation with large doses of heparin and oral anticoagulation with vitamin K antagonists[76, 77]. The underlying pathology is that balloon angioplasty and stent implantation cause endothelial defects and plaque ruptures in the treated coronary artery, resulting in an effect similar to that of acute coronary syndrome: the activation of the coagulation system as a consequence of endothelial disruption[78]. The treatment with heparin and oral anticoagulation was not only ineffective in preventing ST,, but also led to bleeding in large numbers of the treated patients[76].

A **milestone** development in the history of PCI was the subsequent generation of dual antiplatelet therapy (**DAPT**) with ASA and a $P2Y_{12}$ antagonist which, compared to oral anticoagulation, reduced both ST and bleeding complications[76] and became an essential prerequisite for the tremendously successful progress in PCI that has been evident since the 1990s. Thirty-five RCTs, including more than

200,000 patients, tested DAPT and today, about 3.6 million patients are treated with DAPT after ACS or PCI annually in Europe[3].

In 1996, a German group published a study demonstrating the overwhelming superiority of DAPT with ASA and the thienopyridine ticlopidine over a combination of heparin, phenprocoumon, and ASA in patients treated with stent implantation for stable or unstable coronary artery disease (relative risk 0.25 for the primary endpoint cardiac death, MI, repeat revascularisation)[7]. In 1998, a study published by an Anglo-American group concluded that DAPT with ASA and ticlopidine was distinctly better than ASA alone (the primary endpoint reflecting ST occurred in 0.5% vs. 3.0% of patients) and better than ASA and warfarin (2.7% ST) in the prevention of ST, while at the same time reducing bleeding complications with DATP compared to oral anticoagulation (5.5% vs. 6.2% bleeding complications)[8], a finding confirmed in a French trial published in the same year[79]. DAPT has since then been used as a standard treatment for all PCI.

In 2000, the proven effective drug ticlopidine was replaced by the new $P2Y_{12}$ antagonist clopidogrel for the indication of post-PCI DAPT, following positive results showing the comparable efficiency and fewer side effects of clopidogrel compared to ticlopidine. [80]

At about the same time, the development of oral antiplatelet $P2Y_{12}$ receptor antagonists was fundamental not only in the advancement of PCI, but likewise in the treatment of patients with **acute coronary syndrome**, independent of PCI treatment:

In 2001, the CURE study[81] tested DAPT with ASA plus clopidogrel against treatment with ASA alone in 12,562 patients with NSTE-ACS and found a relative risk reduction of 0.8 for the primary endpoint cardiovascular death, nonfatal MI, and stroke (this effect was independent of PCI) at the cost of an increase in major bleeding complications (relative risk 1.38). A subgroup analysis of 2,658 patients treated by PCI in CURE (PCI-CURE study[82]) later confirmed this finding for invasively managed patients.

In acute coronary syndrome, as in PCI, $P2Y_{12}$ receptor antagonists are the standard of care today[9, 83], with the pathophysiological aim being the prevention of the augmentation of existing and the prevention of future thrombi as part of the otherwise natural course of an acute coronary syndrome as a thrombotic disease[1].

Since CURE, the antithrombotic **DAPT** therapy with ASA plus a $P2Y_{12}$ antagonist has been likewise indicated for patients with ACS and patients after PCI, even if

the $P2Y_{12}$ antagonist was further evolved to novel agents while ASA remained unchanged.

In 2007, the TIMI 38 trial[59] compared the novel $P2Y_{12}$ antagonist prasugrel to clopidogrel (with the usual loading dose at that time, but not after CURRENT-OASIS 7[84], of 300 mg.) in patients presenting with all subtypes of ACS scheduled for PCI. The trial concluded that treatment with prasugrel was associated with a reduction of ischemic events, including ST, at the cost of higher rates of bleeding (particularly in patients older than 75, weighing under 60 kg., or with a previous cerebral transitory ischemic event), including life-threatening bleeding, without differences in mortality. Notably, only STEMI patients were randomized and treated before angiography, whereas NSTE-ACS patients obtained the study drug after coronary angiography, i.e., when the coronary anatomy was established and the decision was made that the anatomy was suitable for PCI.

Two years later, the PLATO trial tested another novel $P2Y_{12}$ antagonist, ticagrelor, against clopidogrel in patients again presenting with all subtypes of ACS, i.e., STEMI or NSTE-ACS with specific risk indicators. The primary endpoint (cardiovascular death, MI, stroke) occurred in 9.8% of patients in the ticagrelor arm of the study as compared to 11.7%, with a HR of 0.84, and all-cause mortality was reduced from 5.9% in clopidogrel patients to 4.5%, while ticagrelor was associated with more non-CABG bleeding than clopidogrel. No RCT has tested $P2Y_{12}$ against placebo in STEMI patients treated with primary PCI.

Today, the ESC guidelines recommend antiplatelet therapy for STEMI patients treated by primary PCI with DAPT consisting of ASA plus ticagrelor or prasugrel for up to 12 months[9] and for NSTE-ACS-patients with defined risk markers but without specific contraindications, DAPT with ticagrelor (medically treated patients and patients revascularized with PCI), or prasugrel (PCI only)[83] for 12 months (with exceptions for patients treated by oral anticoagulation for other indications). For stable patients treated with PCI, the ESC guideline recommends treatment with DAPT, including clopidogrel[10], for less than 12 months.

Some studies have evaluated DAPT prolonged beyond 12 months after ACS: The PEGASUS-TIMI-54 trial[85] (60 or 90 mg. of ticagrelor twice daily on top of ASA for 1–3 years, ACS patients only) and the DAPT trial[86] (clopidogrel or prasugrel vs. placebo for an additional 18 months plus ASA after 12 months of DAPT, stable and ACS patients after DES implantation) found fewer ischemic endpoints (Pegasus: HR for cardiovascular death, stroke MI 0.84 for 60 mg. of Ticagrelor twice daily; DAPT trial: HR for ST 0.29; HR for MACE and cerebrovascular events 0.71), but more bleeding (Pegasus: HR for TIMI major bleeding 2.32 for Ticagrelor twice

daily; DAPT trial: HR for moderate or severe bleeding 1.61), without significant differences in mortality in both studies. In summary, there is robust evidence for the effectiveness of the treatment of STEMI and NSTE-ACS patients with DAPT for 12 months. However, there is very little evidence on when to start this treatment.

The question raised in **Papers II and III** is whether it is beneficial to start treatment with the $P2Y_{12}$ antagonist before coronary angiography.

Controversy on pretreatment

Pretreatment is defined[83, 87] as the administration of a $P2Y_{12}$ antagonist before coronary angiography. Despite the lack of definitive evidence regarding its benefit, pretreatment is a common practice[87].

The main debate[88, 89] on pretreatment concerns whether to start DAPT treatment at the first medical contact (or hospital admission), i.e., *before* angiography documents coronary status or *after*[87].

Several pros and cons contribute to the benefit/risk ratio of pretreatment[87].

Potential benefits:

- The increased patency of the infarction related artery (IRA)
- The reduction of periprocedural myocardial infarction
- The prevention of early ST
- The reduction of IRA reocclusion
- The reduction of the need for bail-out GpIIb/IIIa antagonists

Potential harms:

- A higher risk of periprocedural bleeding
- A higher risk of CABG-related bleeding if urgent CABG is required
- A higher risk of ischemic complications if urgent CABG is delayed to wait for $P2Y_{12}$-washout
- The prolongation of hospitalization (waiting for $P2Y_{12}$-washout before CABG)
- Bleeding in inappropriately treated patients, i.e., in patients with negative angiographies and diagnoses other than the initially suspected ACS[90]

Inappropriate treatment (treatment in patients lacking indications or, worse, with contraindications[90-92]) pertains to a substantial fraction of patients in clinical routine and clinical trials: In ATLANTIC[93], 11% of patients were not treated by PCI or

CABG and in ACCOAST[94], only 69% of patients underwent PCI and 6% underwent CABG, while other trials showed that about 10% of patients angiographied for NSTE-ACS did not have significant coronary artery disease[89].

There have only been two major RCTs designed to test pretreatment in ACS directly, the ATLANTIC[93] for STEMI and ACCOAST[94] for NSTE-ACS, neither of which have shown a benefit of pretreatment (see details below). All other evidence has come from subgroup analyses of trials that were not designed to test pretreatment[89].

Guidelines

For **STEMI**, pretreatment (early administration of a $P2Y_{12}$ antagonist) is optional in the 2013 American College of Cardiology /American Heart Association guideline[57] ("*Loading doses of $P2Y_{12}$ inhibitors are provided before or at the time of primary PCI*"), but supported in the 2012 ECS guideline[58] ("*Patients undergoing primary PCI should receive a combination of DAPT with aspirin and an adenosine diphosphate (ADP) receptor blocker, as early as possible before angiography*"), which was the relevant guideline for the study period of Paper II and III. The ESC revised this recommendation in the 2017 guideline and left pretreatment optional ("*A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor),(...), is recommended before (or at latest at the time of) PCI*")[9].

For **Non-STE-ACS**, the 2011 ESC guideline[95] recommended pretreatment "*as soon as possible*" with a class IA indication (based on data from CURE[81], TIMI 38[59], and PLATO[61], although none of these trials was designed to examine the time of administration). The 2015 revision[83] changed this recommendation, following the data generated from the ACCOAST trial[94] (discussed below): *"As the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated. Based on the ACCOAST results, pretreatment with prasugrel is not recommended."*

Finally, in 2017, the ESC turned the clock back with the *focused update on dual antiplatelet therapy in coronary artery disease*[3] and recommended in the *guideline on myocardial revascularisation*[10], as in 2018, pretreatment for patients with a non-STE-ASC with a class IIa-C indication: "*For pretreatment in patients with NSTE-ACS undergoing invasive management, ticagrelor administration (...) or clopidogrel (...) if ticagrelor is not an option, should be considered as soon as the diagnosis is established*." *"Administration of prasugrel in patients in whom*

coronary anatomy is not known is not recommended." The rationale stated in the guideline for this recommendation is that *"pretreatment with ticagrelor was part of the PLATO trial (...) and was associated with an early benefit over clopidogrel*". In other words: For the decision, if one potent $P2Y_{12}$ antagonist (ticagrelor) is indicated for pretreatment, data from a RCT that explicitly examined the potential benefit of pretreatment with another potent $P2Y_{12}$ antagonist against a placebo, and was terminated due to harm, is weighted less in the ESC guideline than data from a RCT on long-term treatment with ticagrelor versus clopidogrel because the latter showed the early benefit of ticagrelor over clopidogrel, without examining pretreatment versus no pretreatment.

In PLATO[61], the median time from the administration of the first dose of the study drug to PCI was 0.25 hour in STEMI patients and 3.93 hours (for ticagrelor) in Non-STE-ACS patients; the study drug was then scheduled for 12 months for both Non-STE-ACS and STEMI patients. In the trial, there were no differences in major bleeding between the ticagrelor-treated patients and the control group, but significant differences in the rate of non-CABG-related major bleeding, and the primary composite endpoint (cardiovascular death, MI, stroke) was positive at 30 days and persistent throughout the study period of one year. The Kaplan-Meier curve presented in the paper started to divide after approximately two weeks. If this division was due to differences between the drugs tested or, as the ESC speculates, due to the timing of administration before PCI, this finding cannot be addressed by this study.

Evidence for pretreatment in STEMI

There has only been one trial designed to study the time of first administration of an ADP antagonist in STEMI patients. I will take a closer look at this study below.

The **ATLANTIC** trial[93], published in 2014, randomized 1,862 patients with suspected ongoing STEMI to either ticagrelor at first medical contact or in the cath lab directly *before* angiography. The mean difference in the administration of ticagrelor in the two arms of the trial was 31 minutes. The co-primary endpoints were the surrogate parameters, the resolution of ST elevation (the proportion of patients having at least a 70% resolution of ST elevation before PCI), and the TIMI III flow grade (the proportion of patients having TIMI III flow in the IRA at angiography) that did not reach significance.

Of note, but not discussed in the paper, was the fact that about 11% of the patients in both groups did not undergo any revascularization, so one might presume that the STEMI diagnosis was incorrect in a majority of these cases. Nevertheless, as all patients received the study drug before angiography, all patients were administered ticagrelor, even those patients who were misdiagnosed and thus lacked an indication for the drug. This strategy contradicts a fundamental advantage of non-pretreatment, namely to avoid treating patients without indications. Several other diseases can hide behind the misdiagnosis of STEMI and some of them will deteriorate with an unindicated antithrombotic treatment, such as aortic dissection[90].

Figure 3: Gothenburg ambulance service

Thus, ATLANTIC is not a study of pretreatment versus non-pretreatment but of early versus late pretreatment and should not be used as proof that pretreatment is safe, as compared to non-pretreatment.

In the ATLANTIC trial, 30 patients died in the prehospital group and 19 died in the in-hospital group at 30 days, a difference reported as non-significant (p = 0.08). For three patients in the in-hospital group and one in the pre-hospital group, no cause of death was available. We do not know if any patient in the misdiagnosed cohort died, nor do we know how many patients developed bleeding among those who were treated inappropriately. The authors concluded that the prehospital administration of ticagrelor "*is safe and may prevent postprocedural stent thrombosis*"[93]. This conclusion does not stand on solid scientific ground[96].

First, the primary endpoint of the trial was neutral. Second, as stated above, the data cannot be used for reasoning about pretreatment versus non-pretreatment. Third, while ATLANTIC reported 30 versus 19 deaths with p = 0.08 as non-significant, one might see a trend of increased mortality at 30 days (odds ratio (OR) of 1.68; 95% confidence interval (CI) 0.94–3.01). Our research group had previously analyzed the data in the supplement and could show that the prehospital administration of ticagrelor is associated with a statistically significant difference in the risk of death within 24 hours (12 deaths in the prehospital group vs. 4 deaths in the in-hospital group, OR 3.18, 95% CI 1.02–9.90, p = 0.046)[96]. Fourth, the ATLANTIC paper reports a significant difference in *definite* ST both at 24 hours and 30 days (at 30 days: OR 0.19, 95% CI 0.04–0.86, p = 0.02). This report should be questioned in five ways:

1. It is problematic to draw a conclusion from a prima vista, statistically positive result for a secondary endpoint in a study with a negative primary endpoint, especially as ATLANTIC did not adjust for multiple comparisons of the secondary endpoints [97-99].
2. The low number of events for definite ST at 30 days (13 in total) entails a considerable risk for a Type I error, as the study was not powered for these low-rate events.
3. There was no difference in *definite or probable* ST at 30 days (OR 1.1, 95% CI 0.60–2.05)[96]. Choosing not to publish this lack of a difference but to instead publish only the result for *definite* ST thrombosis is problematic: In a statement issued in 2007, the Academic Research Committee the "*combination of adjudicated definite and probable stent thrombosis to best characterize this aspect of DES safety*"[100]. PLATO[61], DAPT[86], EXPLORE[101], and dozens of other trials adopted this definition. The main argument is that a ST, an entity with high mortality, is by definition only definite with

angiographic or autopsy confirmation. Sudden cardiac deaths after discharge, with ST as one of the likely causes, are defined as probable.

4. It is biologically highly implausible that a difference of 31 minutes in the time of administration of ticagrelor (with no difference in platelet activity at any time in the ATLANTIC substudy[93]) should reduce ST by fivefold.
5. The study was underpowered for the detection of ST.[102]

While ATLANTIC compared early versus late pretreatment, we compared pretreatment versus non-pretreatment in Papers II and III of this thesis.

A **metalanalysis**[103] published in 2018 by the French ACTION group analyzed seven RCTs with "early versus delayed" $P2Y_{12}$ antagonist administration in STEMI patients scheduled for PCI. The primary endpoint MACE was significantly reduced without an increase in bleeding. All-cause death and cardiovascular death did not differ. Besides ATLANTIC, the following trials were included in the analysis:

- CHAMPION-STEMI[104] (2009), an RCT comparing two drugs for pretreatment, intra venously administered Cangrelor to clopidogrel both within 30 minutes before PCI in ACS patients, including 996 STEMI patients. The study was negative.
- CIPAMI (2012) randomized 337 STEMI patients to either 600 milligrams of clopidogrel in the prehospital phase or the same dose after an angiogram in patients scheduled for PCI. The primary endpoint TIMI 2–3 flow was negative.
- ERASE-MI[105] (2009) was a pilot dose-escalating study testing the then-novel i.v. $P2Y_{12}$ antagonist elinogrel against a placebo in 70 STEMI patients one to 15 minutes before primary PCI. The development of elinogrel was terminated in 2012. All patients received a 600-milligram loading dose of clopidogrel a few minutes after the study drug.
- LOAD&GO[106] tested a 600- versus a 900-milligram loading dose clopidogrel in 168 STEMI patients in the prehospital phase versus 300 milligrams after coronary angiography. Despite the bias of using a lower loading dose for patients who not pretreated, the study was negative regarding the primary endpoint TIMI 3 flow.
- PCI-CLARITY[107] (2005) was a substudy of the CLARITY-TIMI 28[108] trial, which tested clopidogrel versus placebo in thrombolysis for STEMI. The 1,863 patients in PCI-Clarity received 300 milligrams of clopidogrel with thrombolysis and were angiographied after a median delay of three days.
- TRITON-STEMI[109] (2009) analysed the 3,534 patients with STEMI in the TRITON-TIMI 38[59] trial, which randomized them to either clopidogrel or

prasugrel given “as soon as possible” after randomization, but up until one hour after PCI. About 25% were administered the study drug before PCI and 75% received it during PCI. The timing was not randomized. Nearly half of the STEMI patients had a history of more than 12 hours and patients could be included up to 14 days after a STEMI. This practice had previously been criticized[60].

In summary, it is questionable whether this data can support the use of an oral third-generation $P2Y_{12}$ antagonist for pretreatment in primary PCI for STEMI.

In a metaanalysis[110] published in 2012, the same study group analyzed data from five RCTs (8,608 patients) evaluating pretreatment with clopidogrel versus placebo in stable and ACS patients, and from subgroup analyses of four RCTs. The study group found no effect on mortality, but a significant increase in TIMI major bleeding and a significant reduction in MACE, which was mainly due to periprocedural MI.

Evidence for pretreatment in Non-STE-ACS

There has only been one RCT designed to study the time of first administration of an ADP antagonist in non-STE-ACS patients: The **ACCOAST** trial, published in 2013, randomized 4,033 non-STEMI patients scheduled for coronary angiography to prasugrel either before angiography or after angiography when the angiography indicated PCI. A total of 67.8% of the randomized patients were treated by PCI, with a median delay of 4.3 hours from drug administration to PCI. Twenty-five percent were treated medically and 6.2% were treated with CABG, i.e., at least 6.2% were pretreated without an indication. The number of the 25% medically treated patients who had a diagnosis other than ACS at discharge, i.e., the number of those who did not have an indication for pretreatment, was not stated in the paper. There was no difference in the primary composite endpoint (cardiovascular death, MI, stroke, urgent revascularization, glycoprotein IIbIIIa rescue therapy), but major bleeding was highly significantly increased in the pretreatment group: Non-CABG TIMI major bleeding increased three-fold and life-threatening bleeding increased six-fold, which was the cause of the premature termination of the trial.

A criticism of ACCOAST is that the short time from randomization to PCI might have led to an underestimation of the true treatment effect[88], but no interaction was found between the outcome and the time delay to angiography (there was no benefit for pretreatment in patients who waited 48 hours)[102], and this short time interval is comparable to the delay in other randomized studies of NSTE-ACS[89]. Based on this trial, the ESC guideline on NSTE-ACS does not recommend the use

of prasugrel before coronary angiography, i.e., classifies pretreatment with prasugrel as contraindicated (Grade IIIB)[87].

In the 2007 **TRITON-TIM 38** trial[59], a RCT comparing clopidogrel to prasugrel in ACS patients, the patients received prasugrel *after* coronary angiography.

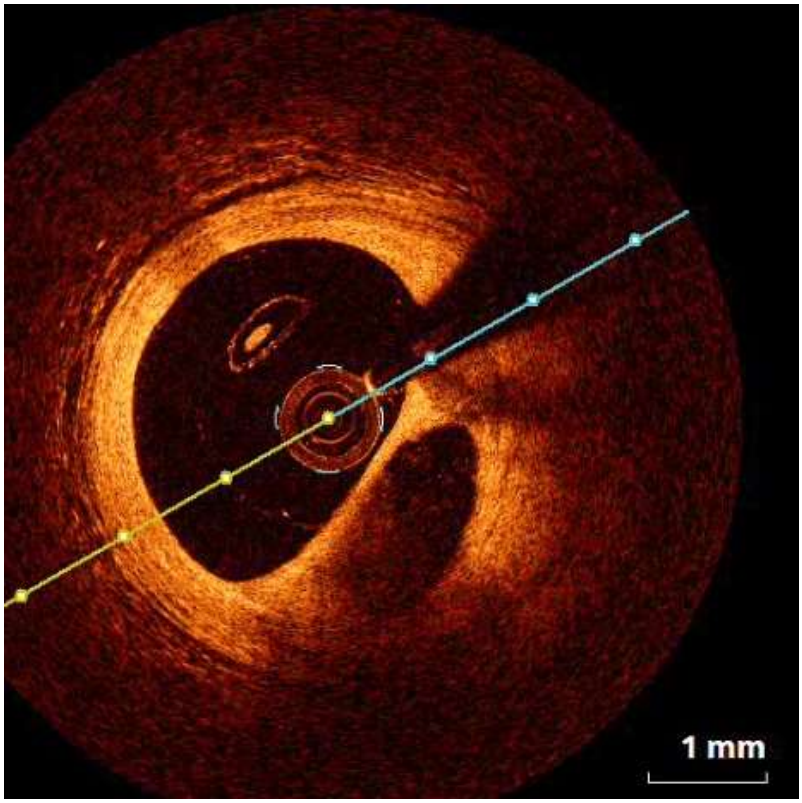

Figure 4: Plaque rupture in the LAD in a NSTE-ACS patient

The **CURE** study is referenced in the ESC 2011 guideline[81]: As stated above, this RCT tested DAPT with ASA plus clopidogrel in 12,562 patients with NSTE-ACS and found a relative risk reduction of 0.8 for the primary endpoint cardiovascular death, nonfatal MI, and stroke at the cost of an increase in bleeding complications, as compared to ASA monotherapy. In the trial, 21.2% of the patients were treated by PCI. Before the CURE study, it was standard practice to give clopidogrel or ticlopidine not to all NSTE-ACS patients but only to patients treated with stent implantation at the end of the procedure in the cath lab, with the intent to prevent ST[88]. In CURE, clopidogrel was administered with a loading dose of 300 milligrams immediately at admission, which led to the adoption of the study protocol as standard clinical practice, i.e., to starting DAPT at admission. So, the question the study answered is whether the DAPT treatment of NSTE-ACS patients

with clopidogrel for an average of nine months (the trial was even positive in an analysis of the first 30 days, even if this was not the primary endpoint) is superior to treatment with ASA alone.

The reason CURE is used as evidence for pretreatment is the substudy on invasively managed patients, i.e., the prospectively designed subgroup analysis of the 21.2% patients treated by PCI (published as the **PCI-CURE** study[82]) that was "*designed to test the hypothesis that, in addition to aspirin, treatment with clopidogrel before PCI is superior to placebo in prevention of major ischemic events afterwards*"[82]. The primary endpoint for PCI-CURE (cardiovascular death, MI, urgent target vessel revascularization within 30 days of PCI) occurred less often in the clopidogrel group. There was no difference between the two groups in cardiovascular mortality within 30 days of PCI.

In CURE, the "vast majority" of patients treated by PCI received open-label thienopyridine "for 2 to 4 weeks" and then went back to the study medication, i.e., clopidogrel or placebo. As the "vast majority" of patients received the same treatment (open-label ticlopidine or clopidogrel) *after* PCI, the difference in outcome at 30 days should be due to the medication administered *before* PCI, i.e., to pretreatment.

Several issues limit the application of this study as evidence for pretreatment today.

1. Anticoagulation: All patients received heparin or low-molecular-weight heparin (LMWH) during their initial hospitalization. The paper does not state the fraction of patients who received heparin or LMWH up to PCI, but because it refers to the FRISC II study[111] on the harm of treatment extending longer than one week, one might assume that this therapy was mostly limited to one week. As the median delay from randomization to PCI was ten days (in 928 patients PCI was done *after* discharge and the median delay to PCI was 49 days with an upper IQR of 106 days), a considerable fraction of patients was only treated with ASA for days to months before PCI. Today, all patients scheduled for invasive treatment receive anticoagulation (mainly LMWH or the selective factor Xa inhibitor fondaparinux) until PCI[83], i.e., the finding that pretreatment lessened the risk of myocardial infarction before PCI in PCI-CURE is not applicable today when anticoagulation treatment before PCI is standard.
2. PCI delay: The delay from randomization to PCI, with a substantial fraction of patients discharged *before* PCI, is not comparable to today's delay time: The time from admission to angiography has internationally decreased substantially since CURE[102] and in Sweden, the vast majority (with some

local exceptions) are now angiographied within three days[2] and discharge before PCI is a rarity. In a subgroup analysis, the primary endpoint was not positive for patients treated by PCI < 72 hours after randomization, who comprised a minority in PCI-CURE.

3. Loading dose: Eighty percent of the patients in PCI-CURE received an open-label thienopyridine after PCI, but the paper does not mention the loading doses. The loading dose is especially important as about 50% of events occur within the first two days after PCI.
4. Due to the different pharmacokinetics, data from clopidogrel should not directly be used as evidence for pretreatment with third-generation $P2Y_{12}$ inhibitors (as shown in the ACCOAST trial[94]).
5. DAPT after PCI: As 80% of the patients in PCI-CURE received an open-label thienopyridine after PCI, 20% of the patients in the placebo group did not receive DAPT at any time. Today, we know that these patients have a very high risk of ST[3].
6. Length of DAPT after PCI: Eighty percent of patients in PCI-CURE received a thienopyridine "for two to four weeks" (median 30 days, IQR 19–33) after PCI, but the paper does not state the exact length of treatment in the two groups[82]. It should thus be kept in mind that, as the open-label treatment after PCI lasted only for two to four weeks, within the primary endpoint's follow-up time of 30 days after PCI in an unknown fraction of patients, the open-label $P2Y_{12}$ therapy was terminated and the study medication (50% placebo) was continued. With today's knowledge, the termination of DAPT two weeks after PCI in an ACS patient is contraindicated[3]. Events extending from PCI to 30 days after PCI can thus not be attributed to pretreatment before PCI.

In PLATO[61], patients were randomized to treatment with ticagrelor or placebo. The study design resembled[88] the design in CURE: Treatment was started directly at admission in all patients, regardless of the final treatment strategy. Sixty-one percent of the 18,624 randomized patients were treated with PCI and the median delay was 2.4 hours for all patients (including STEMI) and 3.8 hours (0.47–48 hours IQR) for the NSTE-ACS patients. In contrast to CURE, all patients received DAPT, i.e., PLATO did not test pretreatment versus no pretreatment. Nevertheless, pretreatment with ticagrelor did not lead to excess bleeding as compared to pretreatment with clopidogrel.

The **CREDO** trial, published one year after CURE in 2002, randomized elective PCI patients to receive a 300-milligram dose of bolus clopidogrel three to 24 hours before PCI, as compared to the placebo (all patients received DAPT in 4 weeks).

Despite the bias introduced by randomization after angiography[89, 102], pretreatment did not reduce ischemic events (or bleeding) at 28 days.[112]

Despite the lack of definite evidence of its benefit and the evidence of its harm with prasugrel[94], pretreatment is general practice[87]. An important question is whether the harm observed with prasugrel in the only trial designed for assessing pretreatment was a class effect or related only to prasugrel. It might be regarded as inconsequential to judge the harm caused by prasugrel as an individual drug effect and, on the other hand, to refer to CURE, a study testing clopidogrel, as evidence for pretreatment with ticagrelor.

Bleeding

Coronary angiography/PCI is both causing bleeding and treating thrombosis:

Coronary angiography and PCI cause bleeding at the access site, a central issue in Paper IV, from the coronary vessel (perforation), a feared complication of all PCI but most commonly occurring in CTO PCI and thus part of Paper I, or in a manner that is not related to the site of access or the site of intervention (e.g., cerebral, abdominal bleeding), i.e., the bleeding is not caused by an iatrogenic, mechanic vessel damage, but related to the antithrombotic medication. This antithrombotic medication is, in part, a prerequisite to prevent the clotting otherwise induced by the catheter, balloon, or stent in all, even stable, patients and, on the other hand, is part of the treatment used for the underlying pathology, i.e., thrombosis, in patients with acute coronary syndrome.

A good portion of interventional cardiology is about preventing bleeding and preventing/treating thrombosis simultaneously. The occurrence and quantity of bleeding under or after coronary angiography and PCI is dependent on numerous factors, such as the access site, the type and dose of anticoagulants used, the indication for PCI (stable patients vs. acute coronary syndrome), acute heart failure or cardiogenic shock (CS), the operator's expertise and PCI technique[113], age, sex, renal function, diabetes, and peripheral vascular disease[114-119]. A fraction of bleeding events is comprised of access-site bleeding, while other bleeding events are unrelated to the access site[114]. Patients who come to the cath lab with acute coronary syndrome and are strongly anticoagulated tend to experience a larger proportion of non-access-related bleeding.

Bleeding, whether it is major or minor[120], access-site-related or non-access-site-related[121, 122], is associated with adverse outcomes, such as death, nonfatal MI, and stroke [114, 117, 120, 123-126].

Bleeding after PCI is a predictor of one-year mortality at a magnitude similar to myocardial infarction after PCI[114, 120, 122]. The reduction of bleeding is shown to be associated with improved survival rates[127, 128] and strategies to reduce bleeding are of the greatest benefit to patients with a high bleeding risk[122], such as STEMI patients.

Vascular access

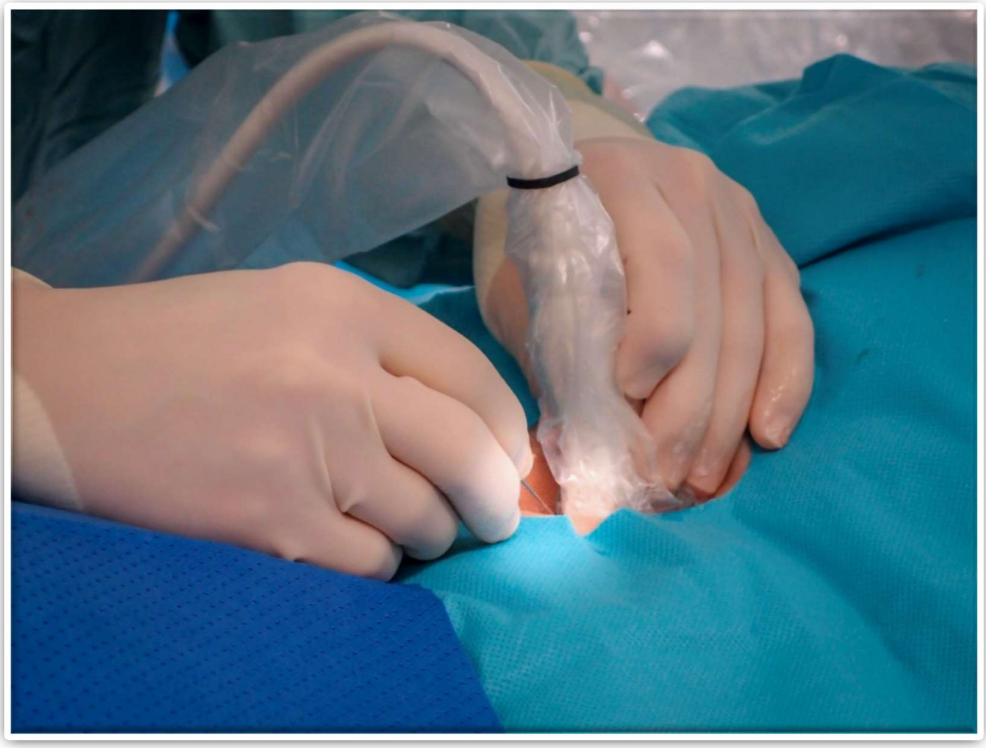

Figure 5: Ultrasound-guided puncture of the femoral artery

While the history of cardiac catheterization began with access in the arm, the annals of PCI start with access in the groin: In the first catheterization of the human heart in a living person, Forssman conducted a self-experiment in 1929[129] in the form of an antecubital venesection for vascular access. The first selective human coronary catheterization, unintentionally performed by Mason Sones on a patient slated for aortography in 1958[130], was likewise achieved via the arteria brachialis. Later, after the Seldinger technique was developed in Sweden in the 1950s[131] and became more widely known in the 1960s, Judkins introduced[130] Seldinger access via the arteria femoralis, thus averting the need for surgical cutdown for vascular access. Femoral access (FA) later became the default method for coronary angiography and intervention. So, since the introduction of PCI in 1977, the traditional approach has been the femoral artery[132, 133].

In 1989, Campeau reported conducting 100 coronary angiographies using the distal radial artery with 5F catheters. In 1992, Ferdinand Kiemeneij, who experienced

severe problems with femoral bleeding in heavily anticoagulated patients scheduled for stenting with a Palmaz-Schatz stent, saw the possibility to reduce bleeding and experimented with and then published on PCI that utilized the radial access (RA) technique[134]. It then took time for transradial PCI to become more widely used in the 21st century.

Since FA was associated with vascular access site complications causing bleeding, ischemia, and death[113, 135-137], the initial intention of the investigation into the feasibility of RA in clinical practice was to reduce access-site-related bleeding. This hope for a reduction in access-site complications and a resulting reduction in bleeding is still the main intention of interventional cardiologists who use the more technically demanding RA.

The patient or medical personnel usually notice subcutaneous bleeding from the radial artery after only a few milliliters and treatment by local compression is mostly easy. In-hospital subcutaneous bleeding from the radial artery can, in sporadic cases, lead to compartment syndrome[138], but is highly improbable to cause hemorrhagic shock. In contrast, in-hospital bleeding from a FA site can be difficult to detect, difficult to treat, and can present with hemorrhagic shock as a first symptom.

Other **advantages** of RA include direct ambulation[139] (bed rest is mandatory after femoral puncture[140]), resulting in earlier or same-day discharge in stable patients same-day [6, 141, 142] and higher patient satisfaction: Fifty percent of RIVAL patients randomized to FA and 90% of those in the RA group would choose RA for their next procedure[143].

A **disadvantage** of the radial puncture, compared to FA, is the limit in the catheter lumen-diameter (specific interventions have to be carried out with FA for this reason) and the higher technical difficulty of vessel puncture and catheter advancement (due to the minor vessel size and arterial spasm[144, 145]) that are evident mainly at the beginning of an operator's learning curve[146], but also for experienced operators in cases of anatomical variations (high radial bifurcation, tortuosity, loops)[6] . The main risk of RA is, mostly asymptomatically, radial artery occlusion[6, 147], with critical distal ischemia being extremely rare, and minor bleeding, which in rare cases can cause compartment syndrome. Pseudoaneurysmata and fistulae in the radial artery are rare complications: In RIVAL[143], 0.2% of patients randomized to RA had an arterial pseudoaneurysm needing closure, compared to 0.4% in the femoral group[143]. To my knowledge, there is no published case of a lethal local complication after RA. It then took more than two decades to gather scientific evidence to prove the initial clinical hypothesis, namely that RA reduces bleeding.

In the first decade of the 21st century, two meta-analyses of several smaller RCTs, published before the larger RCT cited below, showed a reduction in the clinical, significant access-site bleeding by RA[148, 149]. Access-site bleeding, mainly stemming from FA, accounted for 30 to 50% of all bleeding complications in a large study from 2011 (only 8% RA in these patients) [150], i.e., the improvement of arterial access can influence a large fraction of bleeding complications. One crucial component of this development was the refinement of operator skills, equipment, closure devices, and anticoagulation strategies in performing FA PCI over time.

In an analysis of 17,900 patients treated with trans-femoral PCI between 1994 and 2005 at the Mayo Clinic[113], major bleeding decreased over time from 8.4 to 3.5% from first to last tertial and retroperitoneal bleeding decreased from 0.8 to 0.3%. The HR for 30-day mortality, adjusted for baseline and procedural characteristics, was 12.8 for major femoral hematoma and 43.8 for retroperitoneal bleeding.

However, the hypothesis that RA could even further reduce bleeding lived on and since 2011, the interventional community has performed several large RCTs to examine this hypothesis. The first large RCT testing the benefit of RA over FA was the **RIVAL** study[143], which included 7,021 patients with ACS, non-STE-ACS and STEMI, who were analysed in 2011 by intention-to-treat and showed no difference in the composite primary endpoint (death, stroke, MI, non-CABG bleeding at 30 days) or in the secondary endpoint death at 30 days.

But a pre-specified subgroup analysis showed a significant reduction in the primary endpoint in the 1,958 patients STEMI patients included in RIVAL, as well as in the subgroup of centers in the highest tertial of radial volume (mean >146 radial PCI per operator per year). So, one conclusion derived from RIVAL was that a higher RA rate decreases radial complications, but caution is needed in that a very high operator RA rate might lead to more complications in the cases mandating FA, as the operator might lose FA expertise[135].

Concerning bleeding, RIVAL found no significant difference in non-CABG-related major bleeding (access-site-related and non-access-site-related) or in access-site-related major bleeding (0.2% in RA group, 0.3% in FA group, n.s.). Interestingly, in a post-hoc analysis that took the actual bleeding site into account, there were no major access-site bleeds from RA at all compared to 18 major bleeds at the FA point (because of cross-over, subsequent procedures after the index procedure, or femoral IABP insertion.)[143]

In 2012, the next radial study focused on STEMI patients. The multicenter ***RIFLE-STEACS*** [151] study randomized 1,001 patients with STEMI to RA versus

FA in four high-volume centers and found a significant reduction in the primary composite endpoint (cardiac death, stroke, MI, TLR, and bleeding) as well as a statistically significant decrease from 9.2 to 5.2% in the 30-day cardiac mortality rate (in the secondary endpoint).

In 2015, the largest vascular access study, the **MATRIX** study, *Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management* trial [152], was published: Seventy-eight European centers had randomized 8,404 patients with acute coronary syndromes, non-STE-ACS, and STEMI to RA or FA. The first of the two co-primary endpoints, MACE (death, MI, stroke), was negative (p = 0.03 at a co-primary alpha 0,025), while the second, NACE (net adverse clinical events, defined as MACE plus non-CABG BARC[123] major bleeding), was statistically significant (p 0.0092) and clinically significant (RR 0.83, 95% CI 0.73–0.96), driven by a reduction in bleeding and all-cause mortality, with the latter being statistically significant as a predefined secondary endpoint (all-cause mortality 1.6% vs. 2.2%, RR 0.72, 95% CI 0.53–0.99; p = 0.045). The secondary endpoints were all components of the co-primary endpoints, plus cardiovascular mortality and ST, and significance was defined with a two-sided alpha of 5%, i.e., there was no adjustment for multiple comparisons.

In 2016, a **meta-analysis** including 24 RCTs with more than 22,000 patients concluded that RA, compared to FA, reduced all-cause mortality with an OR of 0.71 (95% CI 0.59, 0.87) and a number needed to treat to benefit (NNTB) of 160, MACE with an OR of 0.84 (CI 0.75, 0.94) and a NNTB of 99, major bleeding by a NNTB of 103, and major vascular complications by more than four-fold, with an OR of 0.25 (CI 0.16–0.35) and a NNTB of 117[153].

Accordingly, **a Cochrane review** concluded in 2018 that a "transradial approach for diagnostic CA or PCI (or both) in CAD might reduce short-term NACE, cardiac death, all-cause mortality, bleeding, and access-site complications."[154]

In summary, these trials provided evidence that when utilized by experienced operators, RA for coronary angiography reduced clinical endpoints as well as all-cause mortality[151 152 143]. In many countries[155 156 157 158 159], as in Sweden, radial puncture has, in recent years, evolved as the primary access strategy for coronary angiography and PCI, but large variations between operators, hospitals, and countries still exist[6 160, 161]. Based on this evidence, the current ESC guideline on the management of patients with STEMI includes a strong recommendation for RA[9].

However, despite all the evidence in favor of RA, there is an ongoing controversy[162]. The external validity of the strong evidence for the impact of RA on mortality from the MATRIX study has been questioned [163] and femoral puncture is still the default strategy for the majority of U.S. operators[164], while there is no recommendation for RA in the U.S. STEMI guideline[11].

In summary, there is still a need for more evidence on radial versus femoral access. This is the context for Paper IV.

SWEDEHEART

For this thesis, we used data from the SWEDEHEART registry.

SWEDEHEART[165] is a Swedish national registry of all patients hospitalized for ACS or undergoing for any indication coronary angiography, coronary intervention (PCI or CABG), or valvular intervention. SWEDEHEART was created in 2009 by merging several pre-existing national registries: the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the acute cardiac care registry (Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions, RIKS-HIA), the secondary prevention registry (SEPHIA), and the heart surgery registry. SCAAR was formed in 1998 as a merger of the national coronary angiography and the national angioplasty registries, which were both started in the early 1990s.

All percutaneous coronary procedures, angiographies and PCI, performed in the 27 PCI centers in Sweden are registered in SCAAR. Every procedure is described with approximately 50 variables that report the details of coronary angiography and ~200 variables that report the details of the PCI procedures, including patient characteristics and traditional risk factors. The web-based version that has been used for data entry since 2001 was developed by the Uppsala Clinical Research Centre.

The registry is sponsored by the Swedish Health Authorities and does not receive any funding from commercial interests. Participating hospitals do not receive reimbursement from the registry and cover the costs of data entry themselves.

Approximately 80,000 cases are entered into the registry per year, 40,000 coronary angiographies, 25,000 PCIs, and 7,000 heart surgeries. All patients are informed about their entry into the registry and have the right to decline. SCAAR provides

almost complete coverage of all patients undergoing coronary angiography or PCI, as well as near-100% coverage of ACS patients admitted to coronary care units and approximately 60% coverage of all ACS patients, as some patients are admitted to wards other than specialized coronary care units. The registry data can be merged with data from the National Cause of Death registry[166], which ensures a nearly complete follow-up of mortality data.

Data quality in SWEDEHEART is monitored annually through visits to 20 randomly selected hospitals for the purpose of comparing SWEDEHEART data on 30 to 40 randomly selected patients with the hospitals' records. This comparison of hospital and registry data has previously shown > 95% agreement of data[165].

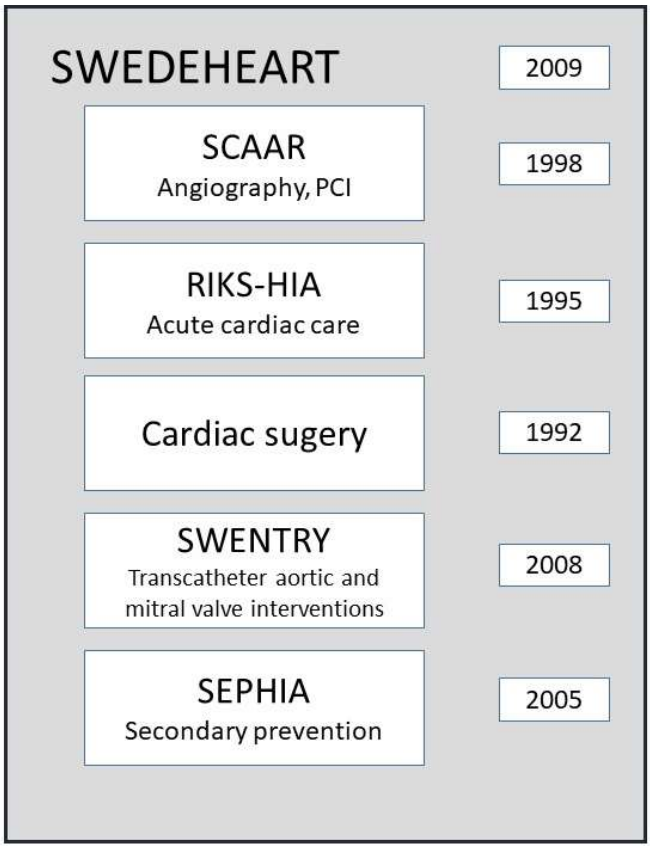

Figure 6: Organisation of the SWEDEHEART registry with the year when the registries were established.

On observation

"At its best a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use."[167]
Austin Bradford Hill, 1984

"Randomized trials have developed such high scientific stature and acceptance that they are accorded an almost religious sanctification...If relied on exclusively they may be dangerous." René Favaloro 1998[168]

Evidence-based medicine is the "*conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients*" [169, 170]. The core principle is to base all policy decisions on the highest-quality scientific data that is openly and objectively derived[171].

So, what is the best evidence and what is the highest-quality scientific data? This thesis builds on observational studies. The knowledge derived from well-designed and adequately conducted randomized clinical trials (RCTs) is currently presumed to represent the **gold standard**[168, 172] in the hierarchy of evidence and thus comprise the most important foundation for the concept of evidence-based medicine[171].

The breakthrough success of the RCT occurred after the success of the British Clinical Research Council's milestone streptomycin trial[173] in 1948[172, 174]. In the U.S. in 1962, the Kefauver-Harris amendment mandated, as a reaction to the Thalidomide tragedy, "adequate and well-controlled investigations" for new pharmaceutics to be authorized, which the FDA interpreted as requiring RCTs for the approval of all new drugs[172]. As an effect of this and similar subsequent requirements in countries such as Europe and Japan, the pharmaceutical industry had by the 1990s passed governments and academic institutions as the leading producer of RCTs[168].

The principal advantage of a sufficiently large RCT, with a properly conducted randomization, is that this RCT is an experiment wherein all differences between the studied groups (known and unknown confounders), other than the studied independent variable (i.e., exposure to the intervention), are due to chance[175]. This leads to a similar distribution of baseline characteristics between the intervention and the control group in many, but not all, RCTs[176]. A **confounder** is a factor that

differs from the studied independent factor and has an effect on the outcome measure, that is imbalanced between the compared exposure groups, that is associated with the disease (as a cause or a proxy of a cause, but not as an effect of the disease), and that is associated with the exposure, but not an effect of the exposure (not a mediator between exposure and outcome). Confounders can exaggerate, mitigate, or reverse a true effect.[177-180]

RCTs have strict inclusion and exclusion criteria and a pre-defined outcome measure. But, as Bradford Hill, one of the founders of randomized trials and a member of the advisory committee of the streptomycin trial, stated later in his life: "*Any belief that the controlled trial is the only way would mean not that the pendulum had swung too far but that it had come right off its hook*."[181]

Limitations of RCT

Well-conducted RCTs are designed to have strong **internal validity**[182-185] (i.e., the extent to which the measure of a treatment effect in a trial can be attributed to the studied intervention in that sample), but due to studying a selected subgroup of the general population, the generalization of the findings to the main population might be problematic or impossible, meaning the RCT might lack **external validity** [167, 182, 186-189] This is even referred to as the difference between **efficacy studies** (explanatory trials testing if, e.g., a drug is beneficial in ideal circumstances) and **effectiveness studies** (pragmatic trials testing if the drug is working in "real-world" clinical practice)[184, 190, 191].

This **generalizability of research** is one of the cornerstones of science[192]: The WHO's international guidelines for health-related research define research as "*activities designed to develop or contribute to generalizable health knowledge*." The problem of generalizability has two sides, with the first relating to the extension of the findings of a trial to a group that has not been studied and the second to the generalization of a group effect measured in a trial to all the different patient groups included in a trial[193]. To paraphrase Bradford Hill: "*At the end of a trial we are not interested (from the scientific viewpoint) in saying that we have found these things to be good for a particular group of patients-for the particular Tom, Dick, and Harry upon whom without thought we inflicted our drugs or our knives. Invariably we wish to generalize from our result—that this treatment is of value in the treatment of a certain type of patient."*[181] Nevertheless, the issue of lacking external validity is "*neglected by current researchers, medical journals, funding agencies, ethics committees, the pharmaceutical industry, and governmental regulators alike*" (P Rothwell 2005[167])

Because of the problem concerning external validity, and other problems, RCTs have important **limitations**[171, 194]**.**

1. External validity:
   1.1. Patients differ from the general population

   The study design "*may call for severe restriction of admissible subjects to a narrow range of characteristics, rather than be a futile attempt to make the subjects representative, in a sampling sense, of the potential target populations*" (Kenneth Rothman[182]). For treatment-evaluation RCTs, often especially medium- to high-risk patients are chosen[187], while patients with low or very high risk, multiple pathologies or severe diseases, or elderly patients [167, 195] tend to be excluded[183, 184, 189, 196]. The finding that a treatment is effective in high-risk patients is not, per se, applicable to low-risk patients[184, 193, 197]. Often, only a small fraction of patients with a disease qualifies for inclusion in a RCT, i.e., many patients with the disease are not eligible based on the inclusion or exclusion criteria [183, 188]

   However, far from all eligible patients are included in the next step. The recruitment of less than 10% of all eligible patients screened at a participating site is common and as a result, patients who are eligible and included in the RCT differ from patients who are eligible but not recruited[167, 187, 198]. Patients who choose not to participate in the RCT testing intervention tend to be more affluent and better educated than the participating patients; the contrary effect occurs in RCTs testing preventive measures in that patients who are more affluent, better educated, and have a healthier lifestyle tend to participate[199]. Inadequate documentation of the characteristics of non-participating eligible patients has been found[187, 199].

   In summary, due to
   a) a trial's eligibility criteria,
   b) the lack of invitations to eligible patients,
   c) the non-participation of centers and clinicians, and
   d) the choice of non-participation made by the invited patients,

   a relevant fraction of patients who are met in "real-world" clinics do not meet the RCT criteria, and in the subfraction of patients meeting the criteria often only a minority is included.[199] **This is why patients included in a**

RCT often do not adequately represent patients in clinical practice[184, 200].

1.2. Treatment differs from the usual treatment

Not only patient selection but also the selection of participating countries (with different patients and different treatment traditions), centers, or physicians can be an issue[167]: Large RCTs are often undertaken predominantly in university hospitals or teaching centers, which might select more skilled caregivers providing higher-quality care (i.e., the trial might produce a greater effect)[184, 199, 201]. On the one hand, the patients screened for participation in these selected centers, often by selected doctors within the centers, already comprise a non-representative subgroup of the total patient population before eligibility and exclusion criteria are reviewed for the trial.[187, 188]

In RCTs testing drugs, repeated feedback from and/or visits by research staff (i.e., more patient-healthcare professional contact than usual) might enhance patient compliance and thus overestimate a drug's effect compared to "real life," i.e., as known in quantum physics[202], the study itself might affect the outcome.[188, 203] **Thus, an effect found in a RCT will not necessarily be the same in the general population.**

2. For practical and financial reasons, RCTs often use **surrogate outcomes**. The only RCT testing the effect of pretreatment with an ADP blocker in STEMI, the ATLANTIC trial[93], includes the resolution of ST elevation and coronary flow as a co-primary endpoint. One of the few RCTs conducted to test PCI with CTO, the EXPLORE trial[23], used LVEF and LVEDV on the MRI as primary outcomes. This strategy does not always correlate with relevant clinical endpoints, as past studies have shown.[204]
3. Many RCTs use **composite outcome measures** that sometimes combine events of very different importance, e.g., a composite outcome of death, nonlethal MI, and rehospitalization that, for any reason, can be driven by rehospitalization alone.
4. RCTs have become a mandatory standard for testing new drugs, but RCTs are more difficult to perform to test other interventions, e.g., surgical therapy[172], which is impossible to double-blind and challenging in terms of sham controls.
5. RCTs usually analyze short study **periods** and **population sizes** that are inadequate to identify severe but rare events[198 188, 196], such as ST, or events that might occur far in the future[194].

6. RCTs often take several years for planning, financing, patient enrollment, follow-up, and analysis and the intervention being tested might already be outdated by the time of publication[205].
7. RCTs today are primarily produced and financed by the pharmaceutical industry[168]. Large RCTs are expensive to perform[172, 184], which influences the choice of what to test and is a relevant factor in drug pricing that might be linked to the observation that industry-sponsored trials are more likely to produce positive results[172, 206, 207] and have shaped contract research organizations as a multibillion-dollar industry that might imply conflicts of interest[207]. One main theoretical advantage of an experimental trial over non-experimental studies, the replicability of experiments, is not realistic to achieve if the experiment costs tens of millions of dollars. With this background, the emergence of randomized registry trials (registry-based RCTs) is a promising development[168, 208, 209], e.g., in Sweden[210, 211].
8. Randomization tends to create a similarity between groups on average, but this tendency, as is always the case with probability, does not guarantee similarity in every trial. In fact, measured confounders can be more similar in observational studies using, e.g., propensity score (PS) matching (see the section on propensity score below for details)[212]. It is therefore mandatory even for RCTs to report on the balancing of baseline variables between the groups[176, 212-214]. The main advantage of RCTs concerns unknown confounders.
9. Non-compliance to the randomized intervention is contradictory to the initial assumption of treatment assignment to only one group[215].
10. Missing data can create severe bias in RCTs and compromise inferences: In the ATLAS ACS-2-TIMI 52 trial[216], which tested the oral factor Xa antagonist rivaroxaban against a placebo in addition to DAPT in patients with recent (enrollment within a week from admission) acute coronary syndrome, the primary efficiency composite endpoint was met (HR 0.84), with an increase in non-CABG TIMI major bleeding (HR 3.96). But the FDA questioned the validity of the trial, in part due to the unusually large amount of missing data (15.5% incomplete follow-up, vital status unknown in 1,117 of 1,294 patients who withdrew consent) and, until today, has not approved Rivaroxaban for the ACS indication[217].

In summary, everything that does not comply with the initial assumptions that all patients in the study are randomly selected from the population of interest and that the groups only differ in the tested independent variable limits the validity of the trial.

Observational studies

Observational studies contribute valid knowledge to the totality of the evidence in medicine for a given scientific question and have certain **advantages** compared to RCT[189, 194]. Non-experimental studies are commonly accepted in the study of disease risk factors and prognosis [200], but even play an important role in comparing the efficacy of therapy: "*By virtue of their size, generalizability, and timeliness, high-quality clinical databases provide up-to-date, accurate estimates of the probabilities of different outcomes in typical settings. (...) The high participation rate in data collection by clinicians from a wide range of hospitals (compared with that in traditional ad hoc research studies) enhances the generalizability of the results and instills ownership of the research, which may encourage uptake of the results into practice (the aim of evidence-based medicine). (...) Finally, the adoption of a clinical database means that research needs no longer be the preserve of a minority of clinicians working in specialist centers. Clinical databases enable clinicians working in typical secondary-care settings to participate, thus enhancing the generalizability of the results*." (Black 1999[218]).

Observational studies are **less expensive** than RCTs; they are typically **faster** to conduct. They have advantages concerning **external validity**, as they often include a broader range of patients in a real-world setting and imply the possibility to study cohorts that are multiple times larger than those of RCTs, as shown in the papers of this thesis, which have all patients angiographied in Sweden for a particular indication over the course of more than a decade as the study base.

Observational studies can be used to attain knowledge **when a RCT cannot be performed** for ethical reasons[188, 194, 219, 220], as demonstrated by Smith in 2003[221], or when a RCT is not conducted for pragmatic or financial reasons, in rare conditions[171, 194] and understudied populations[186], or to understand the effectiveness of actual use.

Because a RCT is usually more expensive for a given clinical hypothesis to test, many important clinical questions remain unanswered by an adequate RCT. Once a new drug has passed a phase III trial and met the regulatory requirements for safety and efficacy, the drug is often not further tested in a large RCT. Observational post-marketing surveillance phase IV trials might find harm that is not found in the smaller phase III RCT concerning rare events[183, 194, 222, 223] or concerning a shift of indication that was not tested in the initial RCT[196] or the treatment of patients with comorbidities that were not included in the RCT[183, 184].

Observational studies using existing databases are a pragmatic method to study large patient cohorts at different sites and different levels of care[183, 188, 224, 225].

Finally, the magnitude of an effect is critical for the decision regarding whether a RCT is needed: If the impact of an intervention is dramatic, observation is adequate because it is unlikely that unknown confounders could explain the outcome, as in insulin therapy for insulin-dependent diabetes, thyroxine for hypothyroidism, penicillin for bacterial infections, or defibrillation for ventricular fibrillation[194].

Methodological improvement in observational studies, primarily the implementation of adequate advanced statistical methods[226-228], has substantially reduced errors in older observational studies, such as those from the 1960s and 1970s[229]. Studies comparing the conclusions of RCTs and observational studies on different clinical topics have shown that the treatment effects measured in case-control or cohort studies did not systematically overestimate or substantially differ from the treatment effect or harm observed in a RCT [226, 228-232]. The results of non-randomized studies best approximate the results of a RCT when both use the same exclusion criteria to generate a more similar population[199, 233].

Criteria have been published to ensure the quality of reporting observational data[234] and to design observational studies and to critically evaluate the quality of the observational data. [235] So, when comparing observational data to RCT, it is essential not just to examine the study method (RCT vs. observational), but to look even closer at the study design[219, 220]. These statistical methods improve the internal validity of observational studies and address problems of observational studies in comparison to RCTs[188].

Limitations of observational studies

Limitations of observational studies[188]:

1. The main limitation (due to study design) is an uneven distribution of factors other than the independent variable that might influence the outcome, i.e., the existence of **confounders**. Confounding can be addressed with adequate statistical methods, given that the confounding factors are known and correctly measured. A method for targeting unknown confounders is discussed below.
2. Not connected to the study design: In observational studies using existing databases, the validity of information (diagnostic, exposure, outcome, confounders) might be less **reliable** compared to that of a well-conducted RCT[200]. Undercoding, overcoding, erroneous coding, or exposure

misclassification might occur. Quality control of the database utilized is a crucial precondition of its use for research[188].

3. RCTs are now expected to be registered at sites like clicicaltrials.org before the trial is started and the methods of major RCTs are published in advance. This includes predefining a hypothesis, endpoints, statistical methods, and subgroup analyses before the data is collected. This is not usually the case in observational studies and hardly controllable when using existing databases, so, for this reason, there is a larger risk of publication bias[236-238] , publication bias "in situ[238]", or "data mining"[178 236, 238, 239], as with multiple testing[240], multiple modelling (testing of different variables for, e.g., regression or instrumental variable analysis)[236, 237, 239], and testing different statistical models for significance in non-randomized studies[199, 237, 241]. Pushing for significance by testing different statistical methods[236] or by conducting multiple tests can also occur in RCTs[242], but due to the reason stated above, it is easier for the reader to identify this limitation in RCT. When databases are screened for "statistically significant" results (medium-sized databases can generate millions of different statistical models[243]) without outlining and publishing this plan in advance, the fraction of false positive results, i.e., the rate of Type I error[178], will be high (much higher than the stated 0.05)[178, 239]. Analyzed from an economic viewpoint by incentive theory, this "data-mining" behavior will occur if it is not controlled for[237]: "*No economist would ever write down a model using the assumptions about individual selflessness that lie behind our statistical methods*" (Glaeser 2006)[236]. This is an important issue that is sometimes overlooked when discussing the advantages and disadvantages of the two study types.

Causation

"I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation.'" Bradford Hill[244']

It is widely accepted in the medical community that only experiments, such as RCTs, can establish **causation**, but not observation, which only identifies associations[220, 245]. But is this true? Do experiments prove causality and do observational studies play no role in establishing causality?

A **cause** is "*an act or event or a state of nature which initiates or permits, alone or in conjunction with other causes, a sequence of events resulting in an* ***effect****. A cause which inevitably produces the effect is sufficient. (...). A specific effect may result from a variety of different sufficient causes. (..) If there exists a component*

cause which is a member of every sufficient cause, such a component is termed a necessary cause." *(Rothman 1976)*[179, 246].
David Hume stated that **causation** is induced logically, not observed empirically[247, 248]. Thus, all conclusions in medical studies are the result of reasoning or ***inference***[248]. ***Deductive*** inference (the truth of the premises guarantees the truth of the conclusion) can never be used to prove a hypothesis in medical science; it can only be used, as Popper stated, to falsify, i.e., reject, a hypothesis[249]. Proof of scientific hypothesis in medical studies, whether experimental or observational, is always facilitated by ***inductive*** inference (the use of premises about examined objects to conclude about comparable (but not similar) objects we have not examined or future events in objects we have examined); the premises can be true but the conclusion nevertheless false. In inductive reasoning, one can only state that a conclusion is probably true[248]. But, to again quote Hill, "I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'"[244].

The causality between smoking and lung cancer, which is no longer scientifically questioned today, was established without a RCT[220, 250-253]. In 1965, the RCT pioneer Hill, who was part of this work[251], published what is now known as the "**Bradford Hill criteria**" [244], a speech containing nine issues (strength, consistency, specificity, temporality, biologic gradient (or dose-response curve), plausibility, coherence, experiment, analogy) to be considered when judging whether to infer causation from the associations observed in *non-experimental* studies. The practical relevance and validity of these criteria have been debated, and it has been emphasized that this speech was not intended as and should not be used as a checklist for establishing causality[246, 247, 254-257]. Several other such criteria were published (e.g., time order, strength, specific, consistency, coherence) in the 1964 Report of the Advisory Committee "Smoking and Health" before and after Hill's criteria[179, 241, 245, 246, 250]. The history of discussion on causation in the natural sciences, leading to and following Hill's speech, has been reviewed elsewhere[246].

Experiments have an advantage in establishing causality regarding a particular studied event, but can, in terms of logic, never give us absolute certainty on a causal effect or the validity of a hypothesis; they can only provide a very high probability. And the underlying aim of every RCT, and the use of the results of a particular experiment for a conclusion about a general principle, is again inductive reasoning. The sharp line often drawn in medical literature between experimental and non-experimental studies' ability to prove a causal relationship (not merely association) is a matter of debate[241, 248].

Some authors see the current **evidence grading system** as biased toward RCT, possibly resulting in the inadequate consideration of non-RCT data.[198 230, 258] Whether the RCT should always be seen as the "gold standard" is to be debated[168, 172]. Actually, the first time[168] the term "gold standard" was used in reference to RCT, the author's conclusion in the NEJM was that "*epidemiological research has become increasingly important because it offers a substitute for the unattainable scientific gold standard of a randomized experimental trial*"[259].

Both RCT and observational studies are susceptible to bias[200]. Observational studies using large health databases can contribute valuable knowledge by studying treatment effects in daily practice in larger and more diverse patient populations with more extended follow-up periods. In this regard, observational studies play an important role in the concept of evidence-based medicine. RCTs and observatory studies should be regarded as complementary.

Types of observational studies

The studies presented in this thesis are prospective cohort studies.

The most standard types of observational studies are case-control studies and cohort studies[171, 178, 183]. Case-control studies identify patients with a disease and compare them to a control group without the disease in analyzing the effect of a treatment or exposure that took place before the condition defined by the inclusion criteria emerged. Thus, case-control studies are **retrospective** by design. On the contrary, inclusion criteria for patients in a cohort study are exposure or non-exposure to an independent variable, e.g., treatment; the two groups are then analyzed for an outcome event that, naturally, occurs after the exposure. Therefore, cohort studies are by definition **prospective** studies, even if both the exposure and the outcome lie in the past at the beginning of the study.

Observational studies can be based on questionnaires, health records, or existing databases[183], as in the studies presented in this thesis.

On statistics

p-value

"*This however, does not mean a blind or exaggerated faith in, or reliance upon, techniques ... In the last analysis it is always the results that matter. Are the observations well and fairly made? Are they good or bad? This is what we want to know and should be told. For it is upon this difference that we shall base our future actions whether it is worthwhile exhibiting the drug or not. The test of significance is of quite secondary importance after we have studied (a) the validity of the trial and the data and (b) the results the data show."* Bradford Hill[182]

"*Consider the sanctified (and sanctifying) magic .05 level. This basis for decision has played a remarkable role in the social sciences and in the lives of social scientists. (...) Its arbitrary unreasonable tyranny has led to data fudging of varying degrees of subtlety from grossly altering data to dropping cases where there "must have been" errors." ..."The primary product of a research inquiry is one or more measures of effect size, not P values."* Jacob Cohen[99]

The p-value is one of the most commonly used statistical measures and is used in all the papers of this thesis. It is defined as *the probability of obtaining the observed result, or more extreme data, given the assumption that the null hypothesis (H_0) is true*[178].

The definition of every p-value begins by assuming that the H_0 is true. One conceptual problem with hypothesis testing in medicine is that this H_0 usually states that there is no difference, not even a very tiny difference, between the groups. As Jacob Cohen stated[99]: "*The null hypothesis, taken literally (and that's the only way you can take it in formal hypothesis testing), is always false in the real world. It can only be true in the bowels of a computer processor running a Monte Carlo study (and even then a stray electron may make it false). If it is false, even to a tiny degree, it must be the case that a large enough sample will produce a significant result and lead to its rejection. So, if the null hypothesis is always false, what's the big deal about rejecting it?*"

So, what does this mean?

One problem with the p-value is that it is easy to misinterpret[260, 261]. For example, a p-value < 0.05 for some measure of a difference in the treatment effect between

two groups can be expressed as follows: *The probability of obtaining the measured result, or a result more extreme (farther away from 0), by chance alone (i.e., if there really is no difference) is less than 5%.* In other words, the Type I error rate α is smaller than 5% *if there really is no effect*, meaning that *if there really is no difference* (H_0 = true), the chance to make a wrong decision and reject H_0 (to make the wrong decision to proclaim a treatment effect, although there really is none) is less than 5% (α < 5%). The p-value even depends on the number of observations; larger cohorts with more observations yield lower p-values.

A p-value of ≤ 0.05 **does NOT mean that** (**false** claims in *italics*, cited in part from[260])[99, 178]:

1. *If p= 0.05, the H_0 has only a 5% chance of being true or, in other words, that there is only a 5% risk that there really is no difference when we proclaim a difference*.
   As the p-value is calculated with the premise that H_0 is true, it cannot at the same time be the probability of H_0 being false. This is a fundamental difference, as the false statement would imply that from only one experiment, we could calculate the probability of our conclusion being an error (a Type I error). Unfortunately, we can't know the likelihood of a Type I error without referring to external evidence or rational thinking, as the Type I error rate α is defined as the probability of a Type I error if H_0 is true, something we rarely know. To calculate the probability of our conclusion being an error, we need to use Bayes' theorem[262, 263].
2. *This "statistically significant" result is of clinical significance*.
   A p-value does **not** tell us anything about the **magnitude** of the effect or the precision of measuring the effect (for this, we have to look at the effect estimate, e.g., a difference between two means, an OR or risk ratio, a correlation coefficient[178, 264], and the CI)[261]. All a p < 0.05 (or a p = 0.000007) tells us is that the effect is **not zero**. The p-value concerns whether there is or is not a difference between the measures of two groups; the p-value is **not** about the size of that difference (for the size of a difference, we need an effect size measure, e.g., mean differences or Cohen's D as the standardized mean differences). Whether a result is clinically significant is highly dependent on the magnitude of the effect, the relevance of the chosen clinical endpoint and, e.g., the side effects of the tested treatment. A treatment decision can usually not be based solely on whether the p-value is significant or not.

3. *The result is, per se,* ***statistically*** *significant.*
   In hypothesis testing, a rejection threshold (at which the p-value of the H_0 is to be rejected) is defined in advance. This is the level of significance α.
   The way to set the value for α, i.e., when to reject H_0, and which result is to be defined as statistically significant, is an individual decision made by the scientist designing a study. In the medical literature, it is, arbitrarily, a tradition to set the limit at 0.05, i.e., 1 in 20. But it is important to remember that this is highly dependent on the circumstances of the study and always comprises a judgment[99] between the probabilities of Type I and Type II errors.
   A scientist doing serial experiments on new drugs desperately seeking treatment for as yet terminally ill children for whom there is no cure would choose an α higher than 5% (accept a high Type I error rate, i.e., accept a higher risk of proposing a treatment as effective when it really is not, as there hitherto is no treatment at all), with the aim to lower the clinically much worse β (Type II error rate, i.e., to reduce the risk of mistaking an actually effective treatment as ineffective). On the contrary, a governmental agency might choose to demand an α lower than 0.05 for a study testing a new me-too drug that is likely to be sold at a higher price than the existing generic, which already has a proven effect.
   This scenario is easily demonstrated by the fact that other specialties choose different levels of α, e.g., physics: An observation of the Higgs particle in 2012 in Switzerland[265] was reported with a $p < 5$ standard deviation, which corresponds to 1 in 3.5 million, instead of 1 in 20 as in medicine. A study is statistically significant when the pre-defined level of significance α is met ($p \leq \alpha$), whatever α is.
   In summary, the level at which the p-value results of medical studies are to be defined as statistically significant can never be calculated mathematically, but can only be defined by clinical judgment.
4. *The value of p doesn´t matter, as long as it is ≤ 0.05.*
   To state that the measured p has a value that is smaller than or equal to the pre-set level of significance only indicates that the H_0 can be rejected according to the pre-set definition. But of course, there is a difference in the weight of evidence if p = 0.05 or 0.00002 or $3x10^{-7}$ as in the Higgs experiment. Both could be expressed as ≤ 0.05, but that would not make much sense.
5. *This is a meaningful level of significance even if we have done multiple analyses.*

P = 0.05 means that there is a chance of 1 in 20 of finding an effect when there really is none. This implies that if we do 20 tests, e.g., 20 subgroup analyses, we expect one "statistically significant" finding, even if there is no effect.[99] This problem with **multiple testing** has to be solved or at least stated in a paper.

If we, on the other hand, calculate a $p > 0.05$ and thus cannot reject the H_0, this **does not prove that the H_0 is true**, i.e., we cannot conclude that there is no difference[99]. As an analogy, if a court that starts a trial with the presumption of innocence fails to prove a defendant guilty, this does not prove the accused innocent.

To summarize, a p-value < 0.05 does NOT imply that there is a 95% chance for the finding to be true. The probability of a research finding being true (the positive predictive value or PPV) can never be estimated by the value of p alone, but only by assessing the prior probability of the finding being true (the R-value, which can only be evaluated with regard to the existing body of evidence), the power of the study (1 minus the Type II error rate, i.e., 1-β), and the level of statistical significance together[263]. An excellent overview of this process was published by Ioannides[263]. This need to relate to the existing body of evidence to estimate the PPV of any study is the most critical argument for why studies like Paper IV (i.e., studies in a field where large, well-conducted other studies exist) are important to conduct and to thus strengthen the total body of evidence.

Propensity score

To make a causal inference from a study to a general population, some average outcome measure (the dependent variable, e.g., a proportion) for a group of patients randomly selected from this general population is compared to the same outcome measure in a similar group of randomly selected patients, while the only relevant difference between the groups should be the allocation to the treatment or control group (the independent variable). Given these assumptions, random selection from the total population, and the similarity (exchangeability) of the groups, causal effects might be concluded as this experiment is the best approximation of the **counterfactual ideal** of allocating a person simultaneously to treatment and control[177].

In a properly designed randomized experiment, allocation to the independent variable, e.g., the treatment or control group, is a matter of chance; no patient-related factor should influence this assignment. In an observational study, there are factors affecting the choice of exposure[178].

As an example, in Paper IV, PCI through the RA was compared to PCI through the FA with death as the outcome measure. The selection of the access site was not randomized, but decided by the treating physician. Several factors can influence this choice, including patient-related factors, such as the diagnosis, comorbidities, hemodynamics, earlier CABG, time of arrival, and the complexity of the planned intervention, social factors, and non-patient related factors, such as the treating physician's preference or skill or the local hospital or national traditions. As a result, because the choice of treatment is influenced by these factors and treatment defines the affiliation to one of the two groups, these factors will be distributed differently in the two compared groups, which conflicts with the initial assumption.

As these factors are not only associated with the exposure (radial vs. femoral) and thus imbalanced across exposure categories, but will even influence the outcome, these are **confounding** variables[177]. In observational studies, different patients have different probabilities of being allocated to one of the independent variables. In Paper IV, the patients are to be treated by either access method, which will influence the outcome measure, meaning differences in the outcome measure might be due to pretreatment differences rather than treatment effects. Different matching procedures exist to increase the balance between the groups and thus reduce this **selection bias[266]**. One of these matching procedures is the ***propensity score***.

The probability of treatment allocation is measured with the ***PS***, which was defined by Rosenbaum and Rubin in 1983 as the "*conditional probability of assignment to a particular treatment given a vector of observed covariates"*[177, 212, 228, 241, 267-269]. **Covariates** are observed characteristics of the patient other than the treatment variable or main independent variable.

The PS is usually calculated by logistic regression analysis for the binary outcome parameter treatment A or treatment B with the measured confounders serving as independent variables. The score is calculated for every patient and lies (like all probabilities) between 0 and 1, with 0.5 being a similar probability for assignment to both groups (given the measured confounders), as would be expected for a randomization procedure[266].

This calculated PS can then be used to adjust for the (known and measured) confounders. The basic idea is that patients in the treatment group and in the control group with the same PS can be considered as if randomly assigned to either group, i.e., to simulate a randomized experiment[269]. For this reason, observational studies using statistical methods for balancing are called quasi-experimental studies. But this is, of course, only true for confounders that are both known and measured (the main advantage of randomization is that it adjusts for both measured

and unmeasured confounders). There are different techniques for how this adjustment can be made in practice, some of which are stated below[212, 228, 266-269]:

1. Matched samples: A patient from treatment group A is paired with a patient or patients from treatment group B (control) with the same (or a similar) PS in a 1:1 or 1:n fashion. In 1:1 matching, unmatched subjects will be discarded from the analysis with a resulting loss of power. Basically, the advantage of this type of matching is that two very similar groups are generated; the disadvantage is that there will be patients who cannot be matched and will have to be excluded from the analysis.
2. Subclassification/stratification
   Patients from both treatment/control groups are divided into subclasses/strata of the same size, according to the PS. Within each strata, the treatment and control patients have the same average PS. It has been shown that five subclasses are sufficient and within the subclasses, there can be a greater balance for known confounders than would have been expected if treatment had been randomized[267]. The outcome measure is then calculated for each interval[266] or the strata can be entered into a regression analysis as a categorical variable. The last method is used in Paper II.
3. Covariate adjustment: The calculated PS is used as a continuous variable in a regression model.

There is no clear consensus on which method to use. In general, choosing between different methods is about choosing between bias and variance: Matching most closely matches pairs and is best at reducing selection bias, but with a resulting reduction in sample size and thus higher variance.[269]. A different method will result in different outcome measures[228].

Recommendations on which variables to include in the PS differ[212, 266]. All variables that are associated with treatment allocation and can influence the outcome measure should be included to avoid omitted variable bias. These confounders are generally measured before treatment assignment[269]. Some authors recommend that variables affected by treatment should be excluded to avoid overmatching[266].

In summary, there are four steps when calculating a PS in a balanced analysis[212]: The first step is to define the model, i.e., to decide which matching technique to use and to select which variables (covariates, confounders) to use in this model. Then, the PS sample is built. The third step is to analyze the degree of balancing accomplished in the sample, e.g., with standardized differences, and adjust the

model if needed. The last step is to estimate the outcome measure in the balanced sample.

PS compared to regression adjustment

PS adjustment has become more popular in recent years[270], while the traditional method of correction is multiple regression analysis of the outcome measure with a treatment indicator and the set of confounders serving as explanatory variables. Comparisons between the two methods have been published[271]. PS adjustment resembles the design of a RCT: In the first step, two matching groups are created (in the RCT by randomization and in PS adjustment in the PS model) and in the second step, the outcome measure is calculated from these groups. On the other hand, regression adjustment is a one-step procedure. This resemblance to a RCT is described as an advantage[241].

Another advantage of PS adjustment is the possibility to report the covariance balance between the two groups before and after correction, something that is not possible with regression analysis[268, 269]. Furthermore, a problem with logistic regression is that the estimates can be incorrect if too many variables have to be included in relation to the number of events: In studies with less than seven events per confounder, PS adjustment is shown to be superior to logistic regression[270] and it has been recommended to have at least 10 events per variable in logistic regression[272]. When the PS is later used as a variable in logistic regression, all confounders are combined into a single variable. PS matching is thus especially suitable in studies with low outcome event rates.

Absolute standardized difference

After adjusting with the PS, it is essential to analyze and report the resulting balance of confounders between the groups. Traditionally, this has often been done by hypothesis testing, resulting in a reported p-value for every confounder[269], but there are relevant arguments against this method[212]: First, multiple testing does not quantify the differences between the groups. Second, in studies with many tested confounders, multiple testing will be a problem. Third, a method for assessing balance should not be dependent on sample size, as the p-value is (smaller samples will appear to have a better balance, as the differences do not reach statistical significance). Finally, the question is whether the studied sample has differences, not if the main population does, so hypothesis testing, which theoretically relates to the main population, is the wrong way to answer. Many statisticians see significance testing to compare the baseline covariates in the two groups of a RCT

or an observational study as an inappropriate method[176, 212, 273]. For these reasons, it is advantageous to use standardized differences.

The **absolute standardized difference** is a standardized **quantification** of the differences between the two groups (calculated using the sample mean and standard deviation: differences between the groups are divided by the pooled standard deviations of the groups) and is shown as a percentage of the standard deviation[180, 212, 269, 274]. An often used rule of thumb is that a standardized difference of less than 10% is a reasonable result after adjustment. When using stratification instead of matching, some authors advocate assessing the balance within each stratum[212].

Instrumental variable analysis

As discussed above, PS adjustment is a statistical method capable of creating a balance of measured confounders in between the two groups of a study that is equivalent to (or better than) the balance that randomization would achieve. What PS adjustment (or logistic regression) cannot do is create a balance of unknown or unmeasured confounders. So, the validity estimates from observational studies that use adjusting techniques as the PS rely on the assumption that there are no unmeasured confounders. This is the fundamental drawback of non-randomized studies: While in a (properly conducted) RCT the assignment to the treatment or control group is due only to chance, in an observational study the decision to treat or not to treat very often depends on the known or unknown confounders. If we take pretreatment with $P2Y_{12}$ antagonists in NSTE-ACS as an example, the decision to prescribe or not to prescribe this medication in an observational study (like Paper III) might depend on a bouquet of clinical variables (e.g., age, diabetes, hemodynamics, co-medication, or other unknown or unmeasured factors) that are also associated with the outcome measure (death). So, in an observational study, if we analyze the outcome as in a RCT by using the fraction of surviving non-pretreated patients as the numerator and the fraction of surviving pretreated patients as the denominator in a standard 2x2 table for the calculation of the OR, the outcome would be biased, and we should not draw causal conclusions.

But what if we could simulate an experiment? What if we found a naturally varying phenomenon that predicts treatment in the way that randomization does, but is not linked to the outcome? Let us, as an example, assume that the decision to pretreat is always made by the attending cardiologist of a hospital and that some of these doctors (group A) mostly prescribe pretreatment (due to reasons not associated with the patient, e.g., due to owned shares of the pharmaceutical company), while other cardiologists (group O) most often do not prescribe pretreatment due to some

personal preference. Other than pretreatment, there are no divergences in treatment habits in the hospital. The result would be, simply stated, that the pretreatment of patients is dependent on which physician is on duty the day the patient is admitted—in other words, due to chance, as with randomization. It would be like a coin flip, only that the variable already is in the data[215].
This is what instrumental variable analysis is about: The aim is to identify a naturally occurring phenomenon in the data that predicts the choice of treatment, but is not (except through the predicted treatment itself) related to the study outcome and thus can be used as an instrument for "**quasi-randomization**." This phenomenon is called **the instrumental variable**, which is an "*unconfounded proxy for a study exposure that can be used to estimate a causal effect in the presence of unmeasured confounding*"[275], meaning it can be used in the **instrumental variable analysis**[191, 215, 271, 275-281].

To qualify as an instrument, a variable has to meet three major criteria:[215, 276, 278]

1. The instrument has to **predict** the treatment a patient received. The strength of the instrument is proportional to the frequency of predicting treatment. This assumption (strength) can be measured and validated[275].
2. The instrument itself should **not be associated with the outcome** other than by the effect of the predicted treatment itself, neither by the
    a. **direct impact** on the outcome (the exclusion restriction) nor by
    b. association through **common causes** (the independence assumption).
    This criterion (validity) cannot be measured and can only be assumed after scientific reasoning[215, 275]

The strength of the instrument (the frequency with which the instrumental variable (IV) predicts the treatment) can be measured with goodness of fit measures, such as the F statistic, or reported as the partial R^2 value (with the partial R^2 indicating the variance that is not explained by the covariates included in the model, i.e. the variance that could be explained by the IV[281]).[215, 282]. The F-statistic (F after statistician Ronald Fisher who described the method in the 1920s as a variance ratio) predicts treatment as a function (dependent variable) of the IV and the covariates (independent variables) by regression analysis with the H_0 that the regression coefficient for the effect of the IV is zero[281]. An IV that is weakly associated with the exposition might lead to reduced precision/high variation in estimates, i.e., wide CIs[281].

Commonly used instruments include geographical criteria[191, 215, 283] (living close to a cath lab in MI studies), physician preference[275, 279, 281] (as in the example above),

or time (as in Paper III)[215, 279, 281]. It is has been recommended to select an IV that is strongly correlated with exposure[276, 277]. IV analysis was well known in economics before it began to be used in the medical sciences[191, 277].

A commonly used technique for outcome analysis in instrumental variable models is the two-stage least squares method. In the context of dichotomous exposures and outcomes, it produces a risk difference estimate[284].

The statistical information is then provided by the patients receiving the treatment correctly predicted by the instrument, which is basically the same as in a RCT, where there are three categories of participating subjects[215, 281]: the compliers (those who follow the intervention recommended by randomization), the non-compliers (those who have already decided to always do or not do the intervention, independent of the randomization), and the defiers (those who, based on character, will always do the opposite). Blinding in a RCT can remove the defiers, but not the non-compliers. In a IV analysis, the compliers, i.e., those who will be predicted by the IV, are called marginal subjects[278]. Statistical information is gained from these marginal patients, as in a RCT, where information in an intention-to-treat analysis (like IV analysis, a measure of association between the treatment *intention* and the outcome[279]) is gained from the patients who comply with the randomized treatment (while assuming that the non-compliant patients are equally distributed by randomization)[215, 278].

With the right variable, IV analysis can be a robust method for adjusting for unknown confounders. The main problem with this technique is to identify an instrument that meets the tree assumptions, wherein assumptions 2a and 2b cannot be measured[277, 282]. It is a scientific judgment based on an unprovable assumption to prefer assumptions 2a and 2b when using IV, or the assumption of the absence of unmeasured confounders when relying solely on the PS or regression analysis[281].

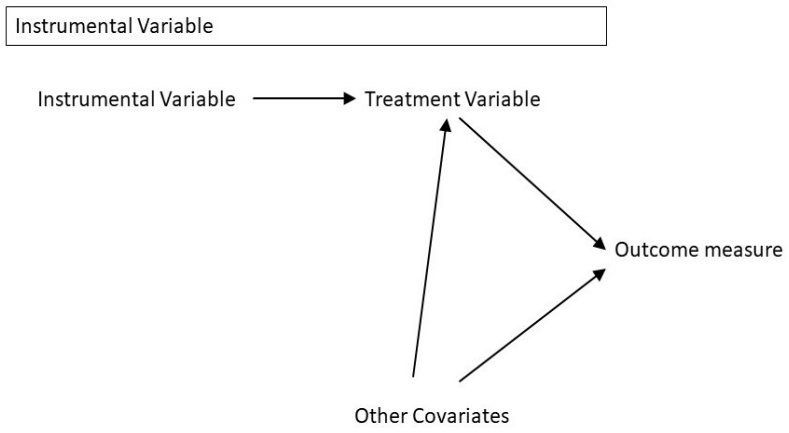

Figure 7: Instrumental Variable

Multilevel models

Every statistical method is only applicable if its underlying assumptions are respected. One of the premises of regression analysis is that all observations are independent of one another. This assumption is violated in the SWEDEHEART database: Patients are treated in hospitals differing in treatment options, treatment availability, traditions, and skill, and hospitals are located in administrative regions with a collaborating structure. Treatment in a particular hospital correlates to where a patient lives, which is known to make a difference in health outcomes[285-287]. In other words, patients are organized in groups and thus not independent from each other as patients treated in one hospital are more alike than patients across different hospitals. The aim of multilevel modeling is to adopt the statistical model to this non-independence of observations.

The term ***multilevel*** describes heterogeneity at different levels in a population[285]: It is well-known in epidemiology that individuals organized in groups are influenced by their group membership. This relationship between individuals and groups can be described as a hierarchical multilayer structure: At level 1, the participants are all individuals. These individuals are sorted into fewer level 2 groups, and the level 2 groups into fewer level 3 groups. In the SWEDEHEART registry, level 1 is comprised of the patients, level 2 of the hospitals, and level 3 of the regions. The structure is hierarchical, as region A influences hospital A and patients A (and vice

versa), but a hospital has much less influence in group A on a patient or a region in group C. Level A individuals have more in common with one another than with individuals in the other groups, i.e., they are **clustered**[285]. Ignoring this cluster effect can result in finding relationships where there are no[285], increasing the risk of a Type I error.

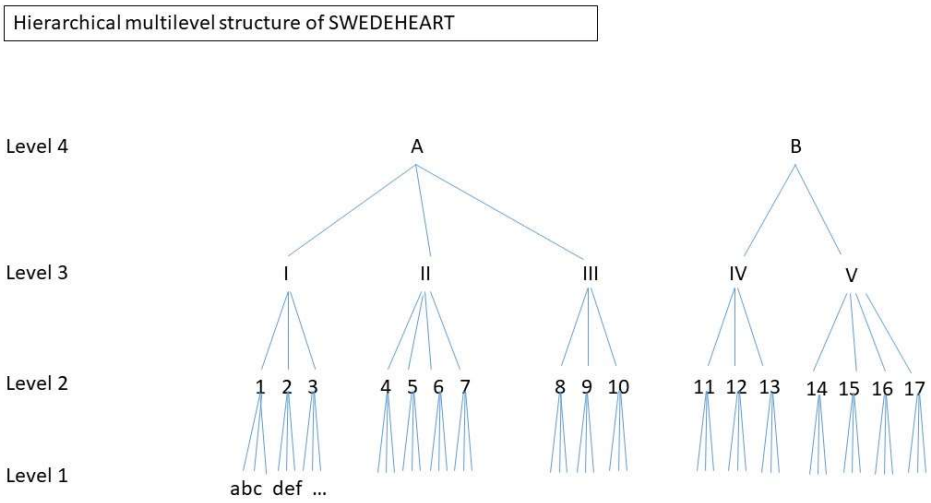

Figure 8: Multilevel model

Multilevel analysis models (or hierarchical modeling, random effects modeling)[178, 287-289] take this hierarchical multilevel structure into account and enable the simultaneous analysis of the effects of group-level variables and individual-level variables on individual outcomes. The primary observational unit (level 1 in Fig. 3) can be, e.g., patients, or coronary vessels, or segments of a coronary vessel, or coronary stents.

This method is applicable to different regression models, such as the logistic regression used for the calculation of a dichotomous outcome like mortality (in Papers II–IV) or the multiple linear regressions that we shall apply to derive an explanation.

In multiple linear univariate regression, we want to find a model that predicts the value of one dependent continuous variable, Y, based on several independent variables, X. Like simple linear regression, multiple regression is a least-squared

method that finds the slope and intercept of a linear regression line that best fits the measured data, i.e., that minimizes the sum of the squares of the discrepancies between the actual and the predicted Y values (i.e., minimizes the distance from the measured values to the regression line). The idea is to create a model that can predict Y from the measured X by finding the point on the regression line that corresponds to the measured X. This model does not consider cluster effects at different levels. What multilevel regression does is to define regression separately for each group in the multilevel database, i.e., to create more than one regression line, e.g., one for every geographic region, while simultaneously examining individual-level predictors[287]. Depending on the model, every one of these regression lines can have fixes (the same) slopes, but random (different) intercepts (thus creating parallel lines), or random intercepts and random slopes.

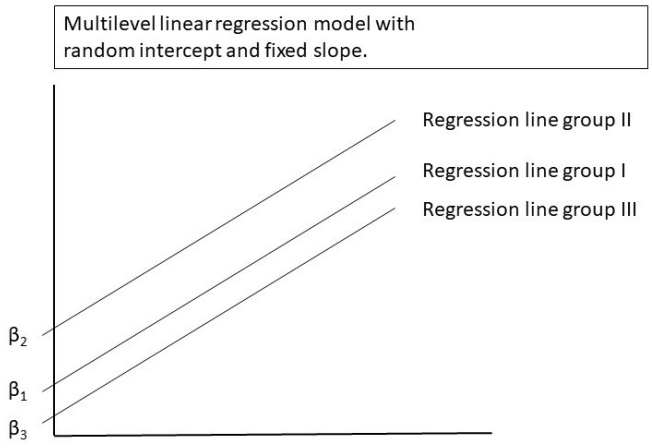

Figure 9: Multilevel linear regression

Median odds ratio

To assess variability in a hospital-level outcome in multilevel models, the median OR (MOR) can be used[290, 291]. The MOR is an effect estimate used in multilevel models that reflects the "*median of the odds ratios that could be obtained by comparing two patients with identical patient-level characteristics from two different, randomly chosen hospitals*"[290, 291] A MOR of 1 indicates no variation between hospitals. [290]

Missing data

A common problem in epidemiological and clinical studies is that not all data that was planned to be collected actually is collected. This data is called missing data[185, 292-294].

This missing data problem also applies to the Swedeheart registry. Some variables in the registry are mandatory (the dataset cannot be saved to the server if not answered), but in some mandatory variables "unknown" is one of the alternative answers that we treated as missing. Other valuables, e.g., creatinine at admission, are optional, which leads to a higher rate of missing data, especially in patients presenting as acute (STEMI, cardiac arrest), wherein creatinine is unknown at presentation. So, the value might not be known, as with creatinine at admission for a STEMI patient or smoking status in an unconscious cardiac arrest patient, or an existing value is merely not entered into the registry to name a few examples. The Swedeheart registry has been expanding over the years, so certain variables that exist today did not exist some years ago, i.e., all data on these variables is missing before a certain time limit. The primary outcome parameter in Papers II to IV, mortality, has virtually no missing data, as it was retrieved from the Swedish National Cause of Death Register that has near complete coverage due to the existence of Swedish personal identification numbers.

Missing data is a significant problem as it can affect the outcome measure in any direction and thus produce misleading conclusions. McNight 2007 explained that[185]: Missing data can "*can affect the quality (i.e., reliability and validity) of our systematic observations. When drawing inferences from our observations, missing data can affect the strength of the study design and the validity of our conclusions about relationships between variables. When we generalize study results, missing data can limit the representativeness of the study sample, the strength and fidelity of interventions, and other study facets such as time or place about which we wish to generalize. Thus, missing data can have a wide range of consequences for the scientific process*."

In spite of this being a common problem, a relevant fraction of studies (e.g., 68% of 262 papers published in 3 epidemiological journals in 2010[294]) do not reporting missing data in a manner that allows reviewers to quantify it[185, 294], even though a recommendation on how to report missing data in observational studies has been published.[234] A thorough discussion of the missing data problem can be found elsewhere[185].

To understand the impact of the missing data on the analysis, the missing data can be described by different patterns of missingness:[292, 295, 296]

1. **Missing completely at random (MCAR):**
   The probability of missingness is **independent of any characteristics** of the studied patients. For example, due to a defect in a laboratory machine that only occurs a few times per month at random, a specific variable is not analyzed in some of the patients. This adds variance, but not bias. This mechanism is most often implausible.

2. **Missing at random (MAR):**
   The probability that a variable is missing **depends only on observed variables**. For example, in a study of different types of ACS, patients presenting with STEMI lack information on creatinine before angiography because there is not sufficient time to analyze the blood sample, whereas all NSTE-ACS patients have information on creatinine. This formulation is liable to misunderstanding, as it is not done "at random" in the common sense. This adds variance with a fixable bias. MAR is incorporated by most statistical models to handle missing data.
3. **Not missing at random (NMAR):**
   The probability that a variable is missing **depends on variables that are incomplete or unknown**. A typical example is that people with a higher income are less likely to state this income; that is, the nonresponse probability depends on values that are missing. In this case, statistical adjustment is not possible, so this variable adds variance with intractable bias[297].

The initial step when dealing with missing data is to try to understand why information is missing and how patients with missing data differ from patients with complete data: If relevant differences exist between patients with complete data and patients with missing data for a specified variable, it can be concluded that the data are not missing completely at random (which leaves MAR and NMAR). The next question is if the observed data can help to predict the missing data, i.e., if the missing data is MAR or NMAR. It is not possible to distinguish between these two by statistical means; that is a scientific decision based on knowledge of the studied field if one may assume that the data is MAR. After addressing these questions, one has to decide which statistical model to use in regard to the missing data.

Models for missing data

There are several approaches to deal with the problem of missing data[295]:

1. Complete case analysis
   In a complete case analysis (CC), only subjects with complete data (all variables observed) are included in the analysis. If the missing data is MCAR, the results of the complete case analysis are unbiased (with increased variance). In the more typical scenarios, where data is not missing completely at random, the results can be biased: When data is MAR, a regression model can be used that controls the variables associated with the missingness. In the case of NMAR data, the bias cannot be controlled.
   In any case, excluding subjects with missing variables (missing data in several variables will have a cumulative effect that can lead to the exclusion of a considerable proportion of the sample) will result in loss of statistical power (with the possible result of an incorrect treatment estimate). In summary, CC has major deficiencies[292, 295, 296], but nevertheless remains the most widely used technique in epidemiologic studies[294].
2. Other techniques, like inverse probability weighting, exist.[294]
3. Imputation
   In imputation models, the missing datum is replaced by a value that is predicted by regression analysis based on the remaining variables of the individual case, so that the complete data set can be analyzed. This implies that the model can only be used for MAR, not for data NMAR (as there are no variables to compute from in multiple regression). An underlying assumption in imputation models is thus that data is MAR (even if this often is not entirely true[297]).
   The Oxford Dictionary defines to impute (which was initially, in the 1940s, called "to allocate"[297]) as "*to calculate something when you do not have exact information, by comparing it to something similar.*" If this imputation process done once for every missing datum, it is called single imputation and when it is done more than once, it is referred to as multiple imputation[298]. At least all the variables included in the analysis should be included in the imputation model[299]. When imputing missing predictor variables, the outcome data should be used in the imputation analysis[295]. In principle, imputing missing data after analyzing its relationship to the existing data is the same process as a paleontologist that imputes missing bones in a discovered dinosaur skeleton to be exhibited[185].

Multiple imputation

Analysis with **multiple imputation** [293, 295, 296, 298-301] follows **three steps**: First, for every existing dataset with missing variables, several new datasets (typically 5–10[301]) are created and the missing value is inserted by using single imputation in each dataset. Second, every dataset is analyzed separately and a point estimate of interest and standard error are extracted. Third, the multiple point

estimates are then combined to obtain an averaged single-point estimate (with the associated CI) using combining rules.[295, 300]
The basic idea behind repeating the single imputation process several times (multiple imputation) is the conclusion that the average of several imputed values better approximates the observed data likelihood[295]: The variability among the imputed values shall reflect an appropriate degree of uncertainty, whereas single imputation techniques fail to account for this uncertainty and produce inappropriate narrow CIs[300]. In 1977 (republished in 2004), Rubin stated that[298]: "*What we really want to impute is the "predictive distribution" of the missing values given then observed values.*"

Multiple imputation, first described in 1977[298], has become more popular in medical research in the last decade[301]: 10 years ago, in 2009, Sterne[296] reported that they searched four medical journals, the NEJM, The Lancet, the BMJ, and the JAMA, for "multiple imputation" in a six-year period from 2002 to 2007 and found 59 articles using this method. In comparison, in the last six years, the NEJM alone has published 92 papers using multiple imputation.

Multiple imputation is a well-documented method, but, as with all statistical tests, its validity depends on the validity of the fundamental assumption, here being primarily that the missing values can be predicted by known values. As is often the case, this can never be definitively proved, but it is essential to understand that the alternative (CC) relies on the mostly far more improbable assumption that the missing data are missing completely at random[294, 299, 300].

Patients and Methods

All four papers of this thesis are based on data from patients included in the SWEDEHEART registry.

Paper I

Study base

The study base consists of all patients who underwent coronary angiography, registered in the SCAAR registry for any indication, in Sweden between 2005 and 2012. Only patients with significant CAD on angiography were included in the study.

Patients with a previous CABG operation were excluded, as well as patients who underwent angiography for ACS in whom the 100% occlusion was located in the same coronary artery as the culprit vessel, in order to differentiate between acute and chronic occlusions. Likewise, we excluded patients who underwent procedures in the same vessel within the previous three months.

Hypothesis

The primary hypothesis of this study is that patients with a CTO found on the coronary angiography for any indication have a higher risk for all-cause mortality, as compared to patients with significant CAD but no CTO.

Outcome measures

The primary outcome measure is all-cause mortality.

Statistics

We used Cox proportional hazards regression models to calculate multivariate-adjusted HRs to analyze the association between CTO and mortality. Because the patients in SCAAR are clustered within the hospitals, the assumption of independence between observations was violated. To adjust for this clustering effect, we used multilevel modeling and shared frailty Cox proportional hazards

regression as the primary model. In addition to CC analysis, we used the multiple imputation method to impute the missing data.

Paper II

Study base

The study base consists of all patients treated by primary PCI for STEMI in Sweden from 2005 to 2016 and registered in the SCAAR. Patients angiographied for suspected STEMI but not revasculated with PCI are not included. A total of 53,146 patients were identified. We excluded patients who did not receive ASA before PCI, patients trombolyzed before PCI, and 1,171 patients with missing data that was not imputed.

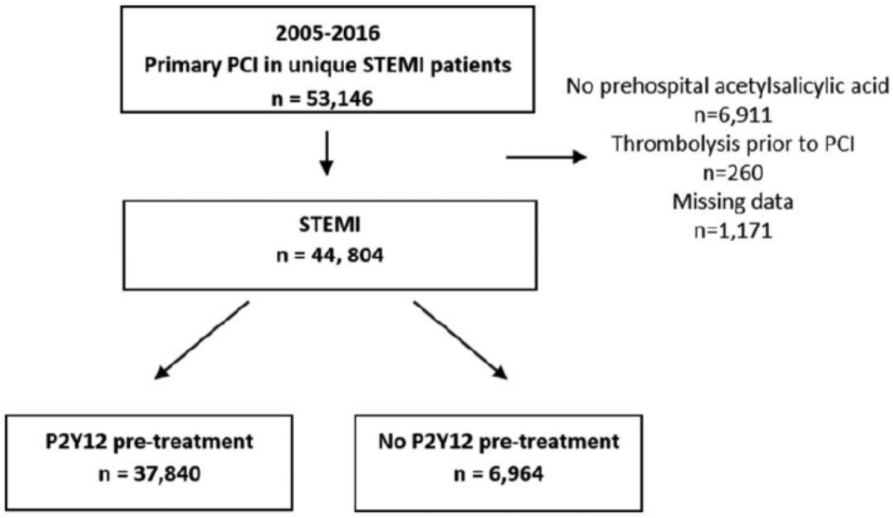

Figure 10: Flowchart for patient selection in Paper II

Hypothesis

The primary hypothesis is that pretreatment with $P2Y_{12}$ antagonists in patients treated with primary PCI for STEMI is associated with a reduced risk of all-cause 30-day mortality, as compared to patients who are not pretreated. Our secondary hypothesis is that pretreatment with $P2Y_{12}$ antagonists is associated with the reduced patency of the infarction-related artery, reduced 30-day definite ST, reduced in-hospital neurological complications, reduced CS, and no difference in in-hospital bleeding.

Outcome measure

The measure for the primary outcome was vital status 30 days after STEMI, as assessed in the Swedish National Cause of Death Register. The secondary outcome measures were the patency of the infarction related artery (assessed by the variable "occlusion" in SCAAR), angiographic confirmed ST within 30 days (this information is routinely entered by a specific variable in SCAAR), neurological complications (variable "neurological complication" in *SCAAR*, CS (variable "Killip IV" in SCAAR or "cardiogenic shock" in RIKS-HIA), and in-hospital bleeding (any of the following variables: puncture site haematoma > 5 cm or pseudo-aneurysm requiring intervention, cardiac tamponade, drop in haemoglobin > 20 g/L, intracranial bleeding, or prolonged compression-treatment (> 6 hours), transfusion, or surgical intervention).

Statistics

We imputed the missing data with multiple imputation generating five data sets. The PS was estimated and entered as a categorical variable based on the quintiles of the propensity score as a covariate into a logistic regression model for each of the five data sets. To account for cluster effects in SWEDEHEART as a hierarchical database, this logistic regression model was a multilevel model with the hospital as the random effect variable. Instrumental variable analysis was not used. The primary outcome measure was the OR for death.

Paper III

Study base

The 69,211 patients treated in Sweden with PCI for NSTE-ACS from 2010 to 2018 were identified in the SWEDEHEART registry. Patients who had not received ASA before PCI and patients with missing data on troponin were excluded. The remaining 64,857 patients were included in the study, 59,894 of whom were pretreated and 4,963 of whom were not pretreated.

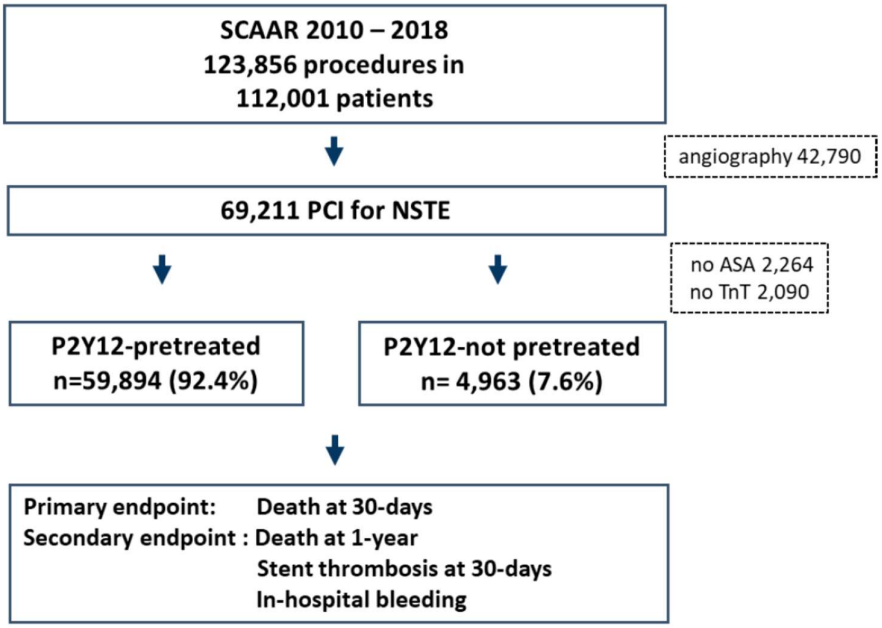

Figure 11: Flowchart for patient selection in Paper III

Hypothesis

Our primary hypothesis is that pretreatment with $P2Y_{12}$ receptor antagonists in patients treated with PCI for NSTE-ACS is associated with a reduced risk of 30-day mortality as compared to patients who were not pretreated. The secondary endpoints were one-year mortality, 30-day definite ST, and in-hospital bleeding.

Outcome measure

The outcome measures were derived according to Paper II.

Statistics

Statistical modeling for all patients was based on Instrumental Variable analysis and the calendar year was used as instrument. The primary and secondary outcomes were evaluated using instrumental variable two-stage least-squares regression analysis. The strength of the instruments was tested with F-statistics and the validity was tested with the Sargan test[302] and by calculating the standardized difference of baseline variables. The PS was not used in this model.

In addition to the main analysis, we prospectively evaluated the impact of a policy change that came into effect in April 2016: The regional board decided to terminate the policy of pretreating ACS patients in the West Swedish district (Västra Götalands Region). We evaluated the effect of this change of clinical practice by

comparing the outcomes before and after in 14,102 of the total 64,857 patients in the study. Of these 14,102 patients, 27.8% were not pretreated.

Paper IV

Study base

A prospective observational cohort study based on SCAAR data from patients angiographied in Sweden for STEMI between 2005 and 2016.

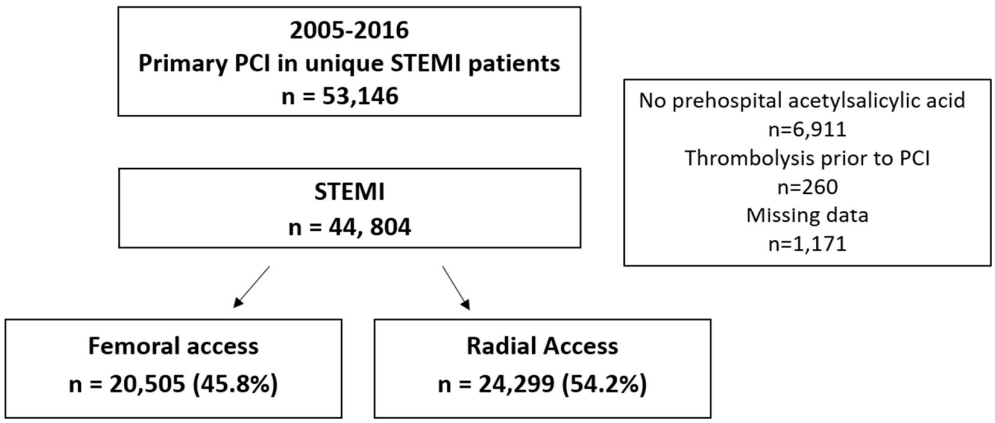

Figure 12: Flowchart for patient selection in Paper IV

Hypothesis

The primary hypothesis of this study is that the use of RA for coronary angiography in STEMI reduces all-cause mortality, compared to FA.

The secondary hypothesis is that the use of RA for coronary angiography in STEMI reduces in-hospital bleeding, stroke, and CS, respectively, compared to FA.

Outcome measures

The primary outcome measure was death of any cause within 30 days as documented in the Swedish population registry. We have no data on the individual cause of death.

The secondary outcome measure was stroke before discharge from hospital, bleeding before discharge as noted in the registry (scale: no, deadly, cerebral, mandating transfusion or operation, unknown, post-discharge bleeding not included) or CS as noted in the registry at discharge from hospital (patients who presented with shock, i.e., the mandatory variable Killip classification, marked as "Killip class IV," are excluded).

Statistics

The patients were stratified into two groups, RA or FA. We adjusted for differences in baseline characteristics with the **propensity score.** The two groups were then compared using **multilevel logistic regression** to account for the hierarchical database. We used **instrumental variable (IV) method** (for adjustment of hidden bias) for sensitivity analysis with the calendar year as the treatment-preference instrument. Regression modeling was performed before and after the exclusion of patients with CS.

Results

Paper I

In the study period, 14,441 of the included patients were found to have a **CTO**, while 75,431 patients had significant coronary disease but no CTO. No patient was lost to follow-up.

The **mortality** rate was higher in patients with a CTO (unadjusted HR: 1.41, 95% CI: 1.35 to 1.48; $p < 0.001$). After adjustment, the CTO remained an independent predictor of long-term mortality (primary model: HR: 1.29; 95% CI: 1.22 to 1.37; $p < 0.001$; CC analysis: HR: 1.27; 95% CI: 1.20 to 1.35; $p < 0.001$). In patients without a CTO, the risk gradually decreased in the study period, while the risk in patients with a CTO increased by 6.6% per year.

PCI was **successful** in 54% of cases and these patients had a lower risk of death compared to patients with whom PCI was unsuccessful (HR: 0.85; 95% CI: 0.73 to 0.98; $p < 0.034$).

Patients with **ACS** had a higher risk associated with CTO compared to patients with stable angina and the risk associated with CTO in patients with STEMI was higher than the risk in NSTE-ACS.

Eighty-three percent of patients had **multivessel** disease, i.e., a stenosis in at least one other coronary vessel than the vessel containing the CTO. Multivessel disease was associated with a higher mortality risk than CTO in a single vessel disease.

There was no difference in risk depending on the **location** of the CTO in one of the three coronary arteries, the left anterior descending, circumflex, or right coronary artery, but a location in a proximal segment had a higher HR compared to a location in a distal segment.
Roughly two-thirds of the patients were 60 to 79 years old, 14.6 % were over 80, and 21.7% were younger than 60. The risk attributable to a CTO decreased by approximately 2% per year of age, i.e., the risk was highest in patients younger than 60 and lowest in patients 80 or older. There was no significant interaction between CTO and the patient's sex.

Paper II

A total of 44,804 patients were included in the study; 58.3% were treated with clopidogrel, 35.3% with ticagrelor, and 5.3% with prasugrel. A total of 84.5% were pretreated. At 30 days, there were 2,488 (5.6%) deaths and 267 (0.6%) STs. Pretreatment was not associated with better survival at 30 days [OR 1.08, 95% CI 0.95–1.24; P = 0.313], reduced IRA occlusion (OR 0.98, 95% CI 0.92–1.05; P = 0.608), decreased ST (OR 0.99, 95% CI 0.69–1.43; P = 0.932), a higher risk of in-hospital bleeding (OR 1.05, 95% CI 0.89–1.26; P = 0.526), or neurological complications (OR 0.66, 0.72, 95% CI 0.43–1.21; P = 0.210).

The interaction test showed no evidence for the effect modification of the type of $P2Y_{12}$ antagonist and pretreatment regarding 30-day mortality, IRA-occlusion, definite ST, in hospital bleeding, or CS.

Paper III

A total of 64,857 patients were included in the study and 43.7% were treated with clopidogrel, 54.5% with ticagrelor and 1.8% with prasugrel. A total of 92.4% of the patients were pretreated, while 7.6% were not. The number of pretreated patients decreased by 2.6% annually between 2010 and 2018.

At 30 days, there were 971 (1.5%) deaths and 101 (0.2%) definite STs. Pretreatment was not associated with better survival at 30 days (OR 1.17; 95% CI 0.66−2.11; P = 0.580), survival at one year (OR 1.34; 95% CI 0.77−2.34; P = 0.297), or decreased ST (OR 0.81; 95% CI 0.42−1.55; P = 0.524).

However, pretreatment was associated with a higher risk of in-hospital bleeding (OR 1.49; 95% CI 1.06−2.12; P = 0.023).

Paper IV

A total of 44,804 patients with STEMI were included in the study, 24,299 with RA and 20,505 with FA.

The two groups had different baseline characteristics with RA patients having generally less traditional risk factors. There were 2,487 (5.5%) deaths, 920 (3.8%) in RA and 1,567 (7.6%) in FA. After adjustment, RA was associated with a lower risk of death (OR 0.70, 95% CI 0.55–0.88, P = 0,025), a lower risk of in-hospital bleeding (OR 0.45, 95% CI 0.25–0.79, P = 0.006), and a lower risk of CS after PCI (OR 0.41, 95% CI 0.24–0.73, P = 0.002).

In patients with STEMI, RA in primary PCI was associated with a reduced risk of 30-day mortality, in-hospital bleeding, and CS.

Discussion and Conclusion

Paper I

We studied the association between CTO and mortality in a large cohort. The SCAAR registry contains the largest CTO cohort reported. We found a moderately increased risk (HR 1.29) for long-term mortality associated with CTO. The divergent mortality trends in patients with and without CTO have not been previously reported.

We found that risk attributable to CTO is highest in younger patients and decreases with advancing age. On the other side, the mortality risk associated with coronary heart disease in general increases with age, so our finding might reflect the increasing importance of other risk factors with advancing age.

In our study, both CAD severity (one-, two-, three-vessel disease) and CTO were independent predictors of mortality. Our data do not support the conception that a CTO merely reflects the additive risk of multivessel versus single-vessel disease (only 17.4 % of CTO patients have single vessel disease, compared to 48.6% in non-CTO patients), as CTO adds an independent risk in all grades of CAD severity. We found no difference in the risk of CTO in one versus in another of the coronary vessels, but the risk was larger in a CTO located in a proximal segment of a vessel compared to a non-proximal segment, and the risk in a distal segment was still larger than the risk in patients without a CTO.

We see these risk gradients as new evidence of a possible causal relationship between CTO and mortality. The reverse conclusion that the revascularization of a CTO could reduce this risk, i.e., have a positive impact on mortality, is still a matter

of debate. As stated in the introduction, there is no convincing evidence for this beneficial effect on mortality. We could show, in coherence with earlier observational data, that successful revascularization is associated with a better prognosis than nonsuccessful revascularisation. This is thought of as limited clinical value, as a medically treated reference group is missing in our study (as well as in other previous studies cited above) and a higher risk in non-successful PCI could reflect a more complex disease or the impact of iatrogenic complications. Bearing this information in mind, the main finding of our study is the strong association between CTO and mortality in the largest CTO cohort yet to be published.

Paper II

In our study, the largest observational research on pretreatment in STEMI to be conducted, pretreatment with $P2Y_{12}$ receptor antagonists was not associated with improved survival in 44,804 patients undergoing primary PCI for STEMI in Sweden between 2005 and 2016. There was also not any difference between pretreatment and non-pretreatment regarding the risk of 30-day definite ST, CS, neurological complications, bleeding, or IRA patency. The last-named finding concerning IRA patency confirms the result of the randomized ATLANTIC[93] trial that there is no beneficial effect of pretreatment with $P2Y_{12}$ antagonists on TIMI flow grade (primary endpoint in ATLANTIC) in STEMI patients managed with primary PCI.

Our study adds real-world data from a national registry with complete coverage of all STEMI patients and thus good external validity to the body of evidence.

A drawback is that we were not able to include patients who were initially, before angiography, diagnosed as STEMI and not treated with PCI, as these patients are not reliably registered in SCAAR. We speculate that the inclusion of these often misdiagnosed patients, many without an indication for DAPT and some with a contraindication for DAPT (e.g., aortic dissection[90]), might have increased the risk of harm for pretreatment. SCAAR does not gather information on the exact timing of $P2Y_{12}$ administration before admission to the cath lab. But we have information on the time of first medical contact, which is comprised mostly of contact with an emergency room or ambulance. We assume a close approximation between the time of first medical contact and the time of drug administration in pretreated

patients. In our study, the median time from first medical contact to PCI is 74 minutes. This time interval correlates with data from the VALIDATE-SWEDEHEART[211] trial, where > 40% of STEMI patients received $P2Y_{12}$ antagonists more than one hour before primary PCI. VALIDATE-SWEDEHEART is a registry-based randomized clinical trial[208] published in 2017 and conducted in Sweden in the timeframe of our study, where information on the time of drug administration was collected as a trial-specific variable in addition to SCAAR data. This time interval is more than the double the pretreatment delay of 31 minutes reported in ATLANTIC.

In conclusion, pretreatment with $P2Y_{12}$ receptor antagonists was safe among patients undergoing primary PCI for STEMI in Sweden between 2005 and 2016, but was not associated with improved survival or improved IRA patency compared to in-cath lab administration.

Our findings independently validate the results of the multicenter randomized ATLANTIC trial.

Paper III

Pretreatment with $P2Y_{12}$ receptor antagonists was not associated with improved survival in 64,857 patients undergoing PCI for NSTE-ACS in Sweden from 2010 to 2018, nor was there a difference in one-year mortality or definite ST. However, pretreatment with $P2Y_{12}$ antagonists was associated with a higher risk of in-hospital bleeding, and the change in practice from routine pretreatment to no pretreatment was associated with a decreased risk of bleeding in patients treated in Västra Götaland Region.

Paper IV

We studied the association between the vascular access site for coronary angiography and the outcome in a large unselected cohort of more than 44,000 STEMI patients. We could show that coronary angiography by RA in patients with STEMI is associated with significantly reduced 30-day mortality, reduced in-hospital bleeding, and less CS, as compared to angiography by FA.

This result is congruent with the recent tree large randomized trials in this field, namely the RIVAL[143], RIFLE-STEACS[151], and MATRIX[152] studies.

There are different explanations for the higher mortality in FA:
First, there are differences in bleeding and its ischemic consequences.
The recently described increased risk for acute kidney injury in FA in ACS patients [303] and STEMI patients[304 305], linked to increased mortality[306], might be another mediator.

Bleeding after PCI is a known predictor of one-year mortality at a magnitude similar to myocardial infarction after PCI [114, 120, 122]. Bleeding is known to be associated with adverse outcomes, including death, nonfatal MI, and stroke [114, 117, 120, 123-126], and the reduction of bleeding is associated with improved survival [127, 128]. This applies to access-site-related and non-access-site-related[121, 122] major and minor bleeding[120].

There are several hypotheses to explain a causality from bleeding to adverse outcomes. A straightforward explanation, which is evident to every interventionist who has lost a patient in this way, is hemorrhagic shock, a life-threatening complication of FA, while a similar complication due to RA bleeding is clearly implausible. But bleeding also induces ischemic complications through the adverse effects of transfusion, the activation of the coagulation cascade, a decreased ischemic threshold in anemia, or the cessation of antithrombotic medication triggered by bleeding[114, 125, 307]. Blood transfusion is an independent predictor of mortality [122, 308, 309]. Endogen erythropoietin might induce a prothrombotic state[310, 311]

To prevent bleeding is an essential aim for every interventional cardiologist. Our data show that RA is associated with a substantially lower risk of in-hospital bleeding as compared to FA. The use of RA in all suitable STEMI patients is an important step to reach this aim.

A novel finding in our study is the association of RA with a substantially lower risk of developing CS. This has not been reported previously and RIVAL, RIFLE, and MATRIX, the largest radial RCTs to date, did not analyze CS as an outcome parameter. Data from observational studies are missing. We excluded patients presenting with CS at admission, i.e., CS at presentation should not have influenced the choice of the access site.

I can only speculate on a causal explanation for RA lowering the risk of developing CS. Different systemic processes, including inflammation[312, 313], are part of the complex pathophysiology of CS. We know that that bleeding and transfusion increase mortality. A systemic inflammatory response triggered by bleeding might comprise one explanation for the association between the RA approach and the decreased risk of CS in our study.

A strong association between CS and bleeding was found in several previous studies[115, 116, 118, 314, 315]: In the CRUSADE registry[314], patients with major bleeding had a risk of CS that was five times higher. The general assumption in the discussion of these studies is that as a causal factor for bleeding, CS explains this association in patients with acute myocardial infarction. Our data point out that the association might be interpreted bidirectional: We identified a plausible mechanism above and there is a plausible temporality due to our study design that excludes the influence of CS on access size, and there might be a consistency with the previous study result as discussed above. This finding is mainly hypothesis generating and further studies are needed.

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References

1. Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF and Braunwald E. *Braunwald's heart disease : a textbook of cardiovascular medicine*; 2019.
2. Swedeheart. Årsrapport. *Årsrapport*.
3. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL and Levine GN. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *European heart journal*. 2018;39:213-260.
4. Tajti P, Burke MN, Karmpaliotis D, Alaswad K, Werner GS, Azzalini L, Carlino M, Patel M, Mashayekhi K, Egred M, Krestyaninov O, Khelimskii D, Nicholson WJ, Ungi I, Galassi AR, Banerjee S and Brilakis ES. Update in the Percutaneous Management of Coronary Chronic Total Occlusions. *JACC Cardiovasc Interv*. 2018;11:615-625.
5. Galassi AR, Werner GS, Boukhris M, Azzalini L, Mashayekhi K, Carlino M, Avran A, Konstantinidis NV, Grancini L, Bryniarski L, Garbo R, Bozinovic N, Gershlick AH, Rathore S, Di Mario C, Louvard Y, Reifart N and Sianos G. Percutaneous Recanalization of Chronic Total Occlusions: 2019 Consensus Document from the EuroCTO Club. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2019.
6. Hamon M, Pristipino C, Di Mario C, Nolan J, Ludwig J, Tubaro M, Sabate M, Mauri-Ferre J, Huber K, Niemela K, Haude M, Wijns W, Dudek D, Fajadet J, Kiemeneij F, European Association of Percutaneous Cardiovascular I, Working Group on Acute Cardiac Care of the European Society of C and Working Group on Thrombosis on the European Society of C. Consensus document on the radial approach in percutaneous cardiovascular interventions: position paper by the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care** and Thrombosis of the European Society of Cardiology. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2013;8:1242-51.
7. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C and Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *The New England journal of medicine*. 1996;334:1084-9.
8. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ and Kuntz RE. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *The New England journal of medicine*. 1998;339:1665-71.
9. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P and Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients

presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European heart journal*. 2018;39:119-177.
10. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R and Zembala MO. [2018 ESC/EACTS Guidelines on myocardial revascularization]. *Kardiologia polska*. 2018;76:1585-1664.
11. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW and American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362-425.
12. Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, Moussa I, Teirstein PS, Dangas G, Baim DS, Selmon M, Strauss BH, Tamai H, Suzuki T, Mitsudo K, Katoh O, Cox DA, Hoye A, Mintz GS, Grube E, Cannon LA, Reifart NJ, Reisman M, Abizaid A, Moses JW, Leon MB and Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation*. 2005;112:2364-72.
13. Brilakis ES. Manual of chronic total occlusion interventions : a step-by-step approach. 2018.
14. Ramunddal T, Hoebers LP, Henriques JP, Dworeck C, Angeras O, Odenstedt J, Ioanes D, Olivecrona G, Harnek J, Jensen U, Aasa M, Jussila R, James S, Lagerqvist B, Matejka G, Albertsson P and Omerovic E. Chronic total occlusions in Sweden--a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *PloS one*. 2014;9:e103850.
15. Tomasello SD, Boukhris M, Giubilato S, Marza F, Garbo R, Contegiacomo G, Marzocchi A, Niccoli G, Gagnor A, Varbella F, Desideri A, Rubartelli P, Cioppa A, Baralis G and Galassi AR. Management strategies in patients affected by chronic total occlusions: results from the Italian Registry of Chronic Total Occlusions. *European heart journal*. 2015;36:3189-98.
16. Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, Gannot S, Samuel M, Weisbrod M, Bierstone D, Sparkes JD, Wright GA and Strauss BH. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *Journal of the American College of Cardiology*. 2012;59:991-7.
17. Werner GS, Gitt AK, Zeymer U, Juenger C, Towae F, Wienbergen H and Senges J. Chronic total coronary occlusions in patients with stable angina pectoris: impact on therapy and outcome in present day clinical practice. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2009;98:435-41.
18. Claessen BE, Dangas GD, Weisz G, Witzenbichler B, Guagliumi G, Mockel M, Brener SJ, Xu K, Henriques JP, Mehran R and Stone GW. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *European heart journal*. 2012;33:768-75.
19. Claessen BE, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjauw KD, Kikkert WJ, Vis MM, Baan J, Jr., Koch KT, de Winter RJ, Tijssen JG, Piek JJ and Henriques JP. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2009;2:1128-34.

20. Sachdeva R, Agrawal M, Flynn SE, Werner GS and Uretsky BF. The myocardium supplied by a chronic total occlusion is a persistently ischemic zone. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2014;83:9-16.
21. Werner GS, Surber R, Ferrari M, Fritzenwanger M and Figulla HR. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. *European heart journal*. 2006;27:2406-12.
22. Sachdeva R, Agrawal M, Flynn SE, Werner GS and Uretsky BF. Reversal of ischemia of donor artery myocardium after recanalization of a chronic total occlusion. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2013;82:E453-8.
23. Henriques JP, Hoebers LP, Ramunddal T, Laanmets P, Eriksen E, Bax M, Ioanes D, Suttorp MJ, Strauss BH, Barbato E, Nijveldt R, van Rossum AC, Marques KM, Elias J, van Dongen IM, Claessen BE, Tijssen JG and van der Schaaf RJ. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI: The EXPLORE Trial. *Journal of the American College of Cardiology*. 2016;68:1622-1632.
24. Werner GS, Martin-Yuste V, Hildick-Smith D, Boudou N, Sianos G, Gelev V, Rumoroso JR, Erglis A, Christiansen EH, Escaned J, di Mario C, Hovasse T, Teruel L, Bufe A, Lauer B, Bogaerts K, Goicolea J, Spratt JC, Gershlick AH, Galassi AR and Louvard Y. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *European heart journal*. 2018;39:2484-2493.
25. Gutierrez-Chico JL and Louvard Y. DECISION-CTO: A "negative" clinical trial? Really? *Cardiology journal*. 2017;24:231-233.
26. Tajti P and Brilakis ES. Chronic Total Occlusion Percutaneous Coronary Intervention: Evidence and Controversies. *J Am Heart Assoc*. 2018;7.
27. Obedinskiy AA, Kretov EI, Boukhris M, Kurbatov VP, Osiev AG, Ibn Elhadj Z, Obedinskaya NR, Kasbaoui S, Grazhdankin IO, Prokhorikhin AA, Zubarev DD, Biryukov A, Pokushalov E, Galassi AR and Baystrukov VI. The IMPACTOR-CTO Trial. *JACC Cardiovasc Interv*. 2018;11:1309-1311.
28. Jones DA, Weerackody R, Rathod K, Behar J, Gallagher S, Knight CJ, Kapur A, Jain AK, Rothman MT, Thompson CA, Mathur A, Wragg A and Smith EJ. Successful recanalization of chronic total occlusions is associated with improved long-term survival. *JACC Cardiovasc Interv*. 2012;5:380-8.
29. Christakopoulos GE, Christopoulos G, Carlino M, Jeroudi OM, Roesle M, Rangan BV, Abdullah S, Grodin J, Kumbhani DJ, Vo M, Luna M, Alaswad K, Karmpaliotis D, Rinfret S, Garcia S, Banerjee S and Brilakis ES. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. *Am J Cardiol*. 2015;115:1367-75.
30. Joyal D, Afilalo J and Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J*. 2010;160:179-87.
31. Yang JH, Kim BS, Jang WJ, Ahn J, Park TK, Song YB, Hahn JY, Choi JH, Lee SH, Gwon HC and Choi SH. Optimal Medical Therapy vs. Percutaneous Coronary Intervention for Patients With Coronary Chronic Total Occlusion - A Propensity-Matched Analysis. *Circulation journal : official journal of the Japanese Circulation Society*. 2016;80:211-7.
32. Jang WJ, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Kim WS, Lee YT and Gwon HC. Long-term survival benefit of revascularization compared with medical therapy in patients

with coronary chronic total occlusion and well-developed collateral circulation. *JACC Cardiovasc Interv*. 2015;8:271-279.
33. Bruckel JT, Jaffer FA, O'Brien C, Stone L, Pomerantsev E and Yeh RW. Angina Severity, Depression, and Response to Percutaneous Revascularization in Patients With Chronic Total Occlusion of Coronary Arteries. *The Journal of invasive cardiology*. 2016;28:44-51.
34. Rossello X, Pujadas S, Serra A, Bajo E, Carreras F, Barros A, Cinca J, Pons-Llado G and Vaquerizo B. Assessment of Inducible Myocardial Ischemia, Quality of Life, and Functional Status After Successful Percutaneous Revascularization in Patients With Chronic Total Coronary Occlusion. *Am J Cardiol*. 2016;117:720-6.
35. Mashayekhi K, Neuser H, Kraus A, Zimmer M, Dalibor J, Akin I, Werner G, Aurel T, Neumann FJ and Behnes M. Successful Percutaneous Coronary Intervention Improves Cardiopulmonary Exercise Capacity in Patients With Chronic Total Occlusions. *Journal of the American College of Cardiology*. 2017;69:1095-1096.
36. Abdullah SM, Hastings JL, Amsavelu S, Garcia-Morales F, Hendrix F, Karatasakis A, Danek BA, Karacsonyi J, Rangan BV, Roesle M, Khalili H, Banerjee S and Brilakis ES. Percutaneous Coronary Intervention of Coronary Chronic Total Occlusions Improves Peak Oxygen Uptake During Cardiopulmonary Exercise Testing. *The Journal of invasive cardiology*. 2017;29:83-91.
37. Patel VG, Brayton KM, Tamayo A, Mogabgab O, Michael TT, Lo N, Alomar M, Shorrock D, Cipher D, Abdullah S, Banerjee S and Brilakis ES. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. *JACC Cardiovasc Interv*. 2013;6:128-36.
38. Brilakis ES, Banerjee S, Karmpaliotis D, Lombardi WL, Tsai TT, Shunk KA, Kennedy KF, Spertus JA, Holmes DR, Jr. and Grantham JA. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). *JACC Cardiovasc Interv*. 2015;8:245-253.
39. Kinnaird T, Kwok CS, Kontopantelis E, Ossei-Gerning N, Ludman P, deBelder M, Anderson R and Mamas MA. Incidence, Determinants, and Outcomes of Coronary Perforation During Percutaneous Coronary Intervention in the United Kingdom Between 2006 and 2013: An Analysis of 527 121 Cases From the British Cardiovascular Intervention Society Database. *Circ Cardiovasc Interv*. 2016;9.
40. Danek BA, Karatasakis A, Tajti P, Sandoval Y, Karmpaliotis D, Alaswad K, Jaffer F, Yeh RW, Kandzari DE, Lembo NJ, Patel MP, Mahmud E, Choi JW, Doing AH, Lombardi WL, Wyman RM, Toma C, Garcia S, Moses JW, Kirtane AJ, Hatem R, Ali ZA, Parikh M, Karacsonyi J, Rangan BV, Khalili H, Burke MN, Banerjee S and Brilakis ES. Incidence, Treatment, and Outcomes of Coronary Perforation During Chronic Total Occlusion Percutaneous Coronary Intervention. *Am J Cardiol*. 2017;120:1285-1292.
41. Dorsam RT and Kunapuli SP. Central role of the P2Y12 receptor in platelet activation. *The Journal of clinical investigation*. 2004;113:340-5.
42. Davi G and Patrono C. Platelet activation and atherothrombosis. *The New England journal of medicine*. 2007;357:2482-94.
43. Packham MA and Rand ML. Historical perspective on ADP-induced platelet activation. *Purinergic signalling*. 2011;7:283-92.
44. Opie LH and Gersh BJ. *Drugs for the Heart : Expert Consult - Online and Print*. Saint Louis: Elsevier Health Sciences; 2014.
45. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *European heart journal*. 2009;30:1964-77.

46. Gaarder A, Jonsen J, Laland S, Hellem A and Owren PA. Adenosine diphosphate in red cells as a factor in the adhesiveness of human blood platelets. *Nature*. 1961;192:531-2.
47. Gachet C, Cattaneo M, Ohlmann P, Hechler B, Lecchi A, Chevalier J, Cassel D, Mannucci PM and Cazenave JP. Purinoceptors on blood platelets: further pharmacological and clinical evidence to suggest the presence of two ADP receptors. *British journal of haematology*. 1995;91:434-44.
48. Storey RF. The P2Y12 receptor as a therapeutic target in cardiovascular disease. *Platelets*. 2001;12:197-209.
49. Born GV, Honour AJ and Mitchell JR. INHIBITION BY ADENOSINE AND BY 2-CHLOROADENOSINE OF THE FORMATION AND EMBOLIZATION OF PLATELET THROMBI. *Nature*. 1964;202:761-5.
50. Abbracchio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Knight GE, Fumagalli M, Gachet C, Jacobson KA and Weisman GA. International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. *Pharmacological reviews*. 2006;58:281-341.
51. Husted S and van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. *Cardiovascular therapeutics*. 2009;27:259-74.
52. Maffrand J-P. The story of clopidogrel and its predecessor, ticlopidine: Could these major antiplatelet and antithrombotic drugs be discovered and developed today? *Comptes Rendus Chimie*. 2012;15:737-743.
53. Hass WK, Easton JD, Adams HP, Jr., Pryse-Phillips W, Molony BA, Anderson S and Kamm B. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *The New England journal of medicine*. 1989;321:501-7.
54. Burnstock G. Purinergic signaling and vascular cell proliferation and death. *Arteriosclerosis, thrombosis, and vascular biology*. 2002;22:364-73.
55. Hollopeter G, Jantzen HM, Vincent D, Li G, England L, Ramakrishnan V, Yang RB, Nurden P, Nurden A, Julius D and Conley PB. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature*. 2001;409:202-7.
56. Savi P, Labouret C, Delesque N, Guette F, Lupker J and Herbert JM. P2y(12), a new platelet ADP receptor, target of clopidogrel. *Biochemical and biophysical research communications*. 2001;283:379-83.
57. Cattaneo M. New P2Y(12) inhibitors. *Circulation*. 2010;121:171-9.
58. Wiviott SD, Antman EM and Braunwald E. Prasugrel. *Circulation*. 2010;122:394-403.
59. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM and Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*. 2007;357:2001-15.
60. Serebruany VL. Timing of thienopyridine loading and outcomes in the TRITON trial: the FDA Prasugrel Action Package outlook. *Cardiovasc Revasc Med*. 2011;12:94-8.
61. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A and Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*. 2009;361:1045-57.

62. Hamberg M, Svensson J and Samuelsson B. Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. *Proceedings of the National Academy of Sciences of the United States of America*. 1975;72:2994-8.
63. Fitzgerald DJ and Fitzgerald GA. Historical lessons in translational medicine: cyclooxygenase inhibition and P2Y12 antagonism. *Circulation research*. 2013;112:174-94.
64. Linné Cv and Salvius L. *Caroli Linnaei ... Species plantarum :exhibentes plantas rite cognitas, ad genera relatas, cum differentiis specificis, nominibus trivialibus, synonymis selectis, locis natalibus, secundum systema sexuale digestas*. Holmiae :: Impensis Laurentii Salvii; 1753.
65. Fuster V and Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation*. 2011;123:768-78.
66. Mueller RL and Scheidt S. History of drugs for thrombotic disease. Discovery, development, and directions for the future. *Circulation*. 1994;89:432-49.
67. Group CCS. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *The New England journal of medicine*. 1978;299:53-9.
68. Lewis HD, Jr., Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, 3rd, Schnaper HW, LeWinter MM, Linares E, Pouget JM, Sabharwal SC, Chesler E and DeMots H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *The New England journal of medicine*. 1983;309:396-403.
69. Chesebro JH, Fuster V, Elveback LR, Clements IP, Smith HC, Holmes DR, Jr., Bardsley WT, Pluth JR, Wallace RB, Puga FJ and et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. *The New England journal of medicine*. 1984;310:209-14.
70. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, Jablonsky G, Kostuk WJ, Melendez LJ, Myers MG and et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *The New England journal of medicine*. 1985;313:1369-75.
71. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet (London, England)*. 1988;2:349-60.
72. Baigent C, Collins R, Appleby P, Parish S, Sleight P and Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *BMJ (Clinical research ed)*. 1998;316:1337-43.
73. Steinhubl SR and Berger PB. Aspirin following PCI: too much of a good thing? *European heart journal*. 2009;30:882-4.
74. Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Salvatori VA, Henderson M, Bonan R and David PR. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. *The New England journal of medicine*. 1988;318:1714-9.
75. Sigwart U, Puel J, Mirkovitch V, Joffre F and Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *The New England journal of medicine*. 1987;316:701-6.
76. Byrne RA, Joner M and Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *European heart journal*. 2015;36:3320-31.
77. Schömig A, Kastrati A, Mudra H, Blasini R, Schühlen H, Klauss V, Richardt G and Neumann FJ. Four-year experience with Palmaz-Schatz stenting in coronary angioplasty

complicated by dissection with threatened or present vessel closure. *Circulation*. 1994;90:2716-2724.
78. Yano Y, Ohmori T, Hoshide S, Madoiwa S, Yamamoto K, Katsuki T, Mitsuhashi T, Mimuro J, Shimada K, Kario K and Sakata Y. Determinants of thrombin generation, fibrinolytic activity, and endothelial dysfunction in patients on dual antiplatelet therapy: involvement of factors other than platelet aggregability in Virchow's triad. *European heart journal*. 2008;29:1729-38.
79. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M, Niccoli L, Oto A, White C, Webb-Peploe M, Van Belle E and McFadden EP. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (fantastic) study. *Circulation*. 1998;98:1597-603.
80. Bertrand ME, Rupprecht HJ, Urban P and Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation*. 2000;102:624-9.
81. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G and Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *The New England journal of medicine*. 2001;345:494-502.
82. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I and Fox KA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet (London, England)*. 2001;358:527-33.
83. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S and Group ESD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European heart journal*. 2016;37:267-315.
84. Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, Granger CB, Jolly S, Joyner CD, Rupprecht HJ, Widimsky P, Afzal R, Pogue J and Yusuf S. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *The New England journal of medicine*. 2010;363:930-42.
85. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Ophuis TO, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E and Sabatine MS. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. *New England Journal of Medicine*. 2015;372:1791-1800.
86. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Jr., Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ and Massaro JM. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *The New England journal of medicine*. 2014;371:2155-66.
87. Sibbing D, Kastrati A and Berger PB. Pre-treatment with P2Y12 inhibitors in ACS patients: who, when, why, and which agent? *European heart journal*. 2016;37:1284-95.

88. Valgimigli M. Pretreatment with P2Y12 inhibitors in non-ST-segment-elevation acute coronary syndrome is clinically justified. *Circulation*. 2014;130:1891-903; discussion 1903.
89. Collet JP, Silvain J, Bellemain-Appaix A and Montalescot G. Pretreatment with P2Y12 inhibitors in non-ST-Segment-elevation acute coronary syndrome: an outdated and harmful strategy. *Circulation*. 2014;130:1904-14; discussion 1914.
90. Hansson EC, Dellborg M, Lepore V and Jeppsson A. Prevalence, indications and appropriateness of antiplatelet therapy in patients operated for acute aortic dissection: associations with bleeding complications and mortality. *Heart (British Cardiac Society)*. 2013;99:116-21.
91. Kohn LT, Corrigan J, Donaldson MS, Institute of M and Committee on Quality of Health Care in A. *To err is human : building a safer health system*. Washington: National Academy Press; 2009.
92. Leape LL. Error in medicine. *Jama*. 1994;272:1851-7.
93. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E and Hamm CW. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *The New England journal of medicine*. 2014;371:1016-27.
94. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, ten Berg JM, Miller DL, Costigan TM, Goedicke J, Silvain J, Angioli P, Legutko J, Niethammer M, Motovska Z, Jakubowski JA, Cayla G, Visconti LO, Vicaut E and Widimsky P. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *The New England journal of medicine*. 2013;369:999-1010.
95. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W and Zahger D. 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*. 2011;32:2999-3054.
96. Redfors B, Angeras O, Petursson P, Ramunddal T and Omerovic E. The ATLANTIC trial does not support the safety of prehospital ticagrelor treatment for patients with ST-elevation myocardial infarction. *International journal of cardiology*. 2015;190:157-8.
97. Freemantle N. Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? *BMJ (Clinical research ed)*. 2001;322:989-91.
98. Multiple Endpoints in Clinical Trials.
99. Cohen J. Things I have learned (so far). *American Psychologist*. 1990;45:1304-1312.
100. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW and Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-51.
101. van der Schaaf RJ, Claessen BE, Hoebers LP, Verouden NJ, Koolen JJ, Suttorp MJ, Barbato E, Bax M, Strauss BH, Olivecrona GK, Tuseth V, Glogar D, Ramunddal T, Tijssen JG, Piek JJ and Henriques JP. Rationale and design of EXPLORE: a randomized, prospective, multicenter trial investigating the impact of recanalization of a chronic total occlusion on left ventricular function in patients after primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. *Trials*. 2010;11:89.

102. Capodanno D and Angiolillo DJ. Pretreatment with antiplatelet drugs in invasively managed patients with coronary artery disease in the contemporary era: review of the evidence and practice guidelines. *Circ Cardiovasc Interv*. 2015;8:e002301.
103. Bellemain-Appaix A, Begue C, Bhatt DL, Ducci K, Harrington RA, Roe M, Wiviott SD, Cucherat M, Silvain J, Collet JP, Bernasconi F and Montalescot G. The efficacy of early versus delayed P2Y12 inhibition in percutaneous coronary intervention for ST-elevation myocardial infarction: a systematic review and meta-analysis. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2018;14:78-85.
104. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV, Jr., Montalescot G, Mahaffey KW, Kleiman NS, Goodman SG, Amine M, Angiolillo DJ, Becker RC, Chew DP, French WJ, Leisch F, Parikh KH, Skerjanec S and Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. *The New England journal of medicine*. 2009;361:2318-29.
105. Berger JS, Roe MT, Gibson CM, Kilaru R, Green CL, Melton L, Blankenship JD, Metzger DC, Granger CB, Gretler DD, Grines CL, Huber K, Zeymer U, Buszman P, Harrington RA and Armstrong PW. Safety and feasibility of adjunctive antiplatelet therapy with intravenous elinogrel, a direct-acting and reversible P2Y12 ADP-receptor antagonist, before primary percutaneous intervention in patients with ST-elevation myocardial infarction: the Early Rapid ReversAl of platelet thromboSis with intravenous Elinogrel before PCI to optimize reperfusion in acute Myocardial Infarction (ERASE MI) pilot trial. *Am Heart J*. 2009;158:998-1004.e1.
106. Ducci K, Grotti S, Falsini G, Angioli P, Liistro F, Mando M, Porto I and Bolognese L. Comparison of pre-hospital 600 mg or 900 mg vs. peri-interventional 300 mg clopidogrel in patients with ST-elevation myocardial infarction undergoing primary coronary angioplasty. The Load&Go randomized trial. *International journal of cardiology*. 2013;168:4814-6.
107. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Lewis BS, Murphy SA, McCabe CH and Braunwald E. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *Jama*. 2005;294:1224-32.
108. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH and Braunwald E. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *The New England journal of medicine*. 2005;352:1179-89.
109. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH and Antman EM. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet (London, England)*. 2009;373:723-31.
110. Bellemain-Appaix A, O'Connor SA, Silvain J, Cucherat M, Beygui F, Barthelemy O, Collet JP, Jacq L, Bernasconi F and Montalescot G. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Jama*. 2012;308:2507-16.
111. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease. Investigators. *Lancet (London, England)*. 1999;354:701-7.
112. Steinhubl SR, Berger PB, Mann JT, 3rd, Fry ET, DeLago A, Wilmer C and Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *Jama*. 2002;288:2411-20.

113. Doyle BJ, Ting HH, Bell MR, Lennon RJ, Mathew V, Singh M, Holmes DR and Rihal CS. Major femoral bleeding complications after percutaneous coronary intervention: incidence, predictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. *JACC Cardiovasc Interv*. 2008;1:202-9.
114. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB, 3rd, Ohman EM and Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *Journal of the American College of Cardiology*. 2007;49:1362-8.
115. Numasawa Y, Kohsaka S, Ueda I, Miyata H, Sawano M, Kawamura A, Noma S, Suzuki M, Nakagawa S, Momiyama Y and Fukuda K. Incidence and predictors of bleeding complications after percutaneous coronary intervention. *Journal of cardiology*. 2017;69:272-279.
116. Young K, Earl T, Selzer F, Marroquin OC, Mulukutla SR, Cohen HA, Williams DO, Jacobs A, Kelsey SF and Abbott JD. Trends in major entry site complications from percutaneous coronary intervention (from the Dynamic Registry). *Am J Cardiol*. 2014;113:626-30.
117. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ and Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. *Journal of the American College of Cardiology*. 2010;55:2556-66.
118. Mehta SK, Frutkin AD, Lindsey JB, House JA, Spertus JA, Rao SV, Ou FS, Roe MT, Peterson ED and Marso SP. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. *Circ Cardiovasc Interv*. 2009;2:222-9.
119. Manoukian SV. Predictors and Impact of Bleeding Complications in Percutaneous Coronary Intervention, Acute Coronary Syndromes, and ST-Segment Elevation Myocardial Infarction. *American Journal of Cardiology*. 2009;104:9C-15C.
120. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schomig A and Kastrati A. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *Journal of the American College of Cardiology*. 2008;51:690-7.
121. Yatskar L, Selzer F, Feit F, Cohen HA, Jacobs AK, Williams DO and Slater J. Access site hematoma requiring blood transfusion predicts mortality in patients undergoing percutaneous coronary intervention: data from the National Heart, Lung, and Blood Institute Dynamic Registry. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2007;69:961-6.
122. Chhatriwalla AK, Amin AP, Kennedy KF, House JA, Cohen DJ, Rao SV, Messenger JC and Marso SP. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *Jama*. 2013;309:1022-9.
123. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG and White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736-47.
124. Ben-Yehuda O and Redfors B. Validation of the Bleeding Academic Research Consortium Bleeding Definition: Towards a Standardized Bleeding Score. *Journal of the American College of Cardiology*. 2016;67:2145-2147.

125. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA and Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114:774-82.
126. Lindsey JB, Marso SP, Pencina M, Stolker JM, Kennedy KF, Rihal C, Barsness G, Piana RN, Goldberg SL, Cutlip DE, Kleiman NS and Cohen DJ. Prognostic impact of periprocedural bleeding and myocardial infarction after percutaneous coronary intervention in unselected patients: results from the EVENT (evaluation of drug-eluting stents and ischemic events) registry. *JACC Cardiovasc Interv*. 2009;2:1074-82.
127. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ, Bassand JP, Wallentin L, Joyner C and Fox KA. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *The New England journal of medicine*. 2006;354:1464-76.
128. Mehran R, Lansky AJ, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Wong SC, Nikolsky E, Gambone L, Vandertie L, Parise H, Dangas GD and Stone GW. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet (London, England)*. 2009;374:1149-59.
129. Meyer JA. Werner Forssmann and catheterization of the heart, 1929. *The Annals of thoracic surgery*. 1990;49:497-9.
130. Bruschke AV, Sheldon WC, Shirey EK and Proudfit WL. A half century of selective coronary arteriography. *Journal of the American College of Cardiology*. 2009;54:2139-44.
131. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography. A new technique. *Acta radiologica Supplement*. 1952;434:47-52.
132. Gruntzig AR, Senning A and Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *The New England journal of medicine*. 1979;301:61-8.
133. Barton M, Gruntzig J, Husmann M and Rosch J. Balloon Angioplasty - The Legacy of Andreas Gruntzig, M.D. (1939-1985). *Frontiers in cardiovascular medicine*. 2014;1:15.
134. Kiemeneij F and Laarman GJ. Percutaneous transradial artery approach for coronary stent implantation. *Catheterization and cardiovascular diagnosis*. 1993;30:173-8.
135. Azzalini L, Tosin K, Chabot-Blanchet M, Avram R, Ly HQ, Gaudet B, Gallo R, Doucet S, Tanguay JF, Ibrahim R, Gregoire JC, Crepeau J, Bonan R, de Guise P, Nosair M, Dorval JF, Gosselin G, L'Allier PL, Guertin MC, Asgar AW and Jolicoeur EM. The Benefits Conferred by Radial Access for Cardiac Catheterization Are Offset by a Paradoxical Increase in the Rate of Vascular Access Site Complications With Femoral Access: The Campeau Radial Paradox. *JACC Cardiovasc Interv*. 2015;8:1854-64.
136. Johnson LW, Lozner EC, Johnson S, Krone R, Pichard AD, Vetrovec GW and Noto TJ. Coronary arteriography 1984–1987: A report of the registry of the society for cardiac angiography and interventions. I. Results and complications. *Catheterization and cardiovascular diagnosis*. 1989;17:5-10.
137. Eisen A, Kornowski R, Vaduganathan M, Lev E, Vaknin-Assa H, Bental T, Orvin K, Brosh D, Rechavia E, Battler A and Assali A. Retroperitoneal bleeding after cardiac catheterization: a 7-year descriptive single-center experience. *Cardiology*. 2013;125:217-22.
138. Tizon-Marcos H and Barbeau GR. Incidence of compartment syndrome of the arm in a large series of transradial approach for coronary procedures. *Journal of interventional cardiology*. 2008;21:380-4.
139. Wiper A, Kumar S, MacDonald J and Roberts DH. Day case transradial coronary angioplasty: a four-year single-center experience. *Catheterization and cardiovascular*

interventions : official journal of the Society for Cardiac Angiography & Interventions. 2006;68:549-53.
140. Bangalore S and Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;124:e147-56.
141. Bertrand OF, De Larochelliere R, Rodes-Cabau J, Proulx G, Gleeton O, Nguyen CM, Dery JP, Barbeau G, Noel B, Larose E, Poirier P and Roy L. A randomized study comparing same-day home discharge and abciximab bolus only to overnight hospitalization and abciximab bolus and infusion after transradial coronary stent implantation. *Circulation*. 2006;114:2636-43.
142. Ziakas AA, Klinke BP, Mildenberger CR, Fretz DE, Williams EM, Kinloch FR and Hilton j GJ. Safety of same-day-discharge radial percutaneous coronary intervention: a retrospective study. *Am Heart J*. 2003;146:699-704.
143. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, Budaj A, Niemelä M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD, Chrolavicius S and Mehta SR. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *The Lancet*. 2011;377:1409-1420.
144. Pristipino C, Roncella A, Trani C, Nazzaro MS, Berni A, Di Sciascio G, Sciahbasi A, Musaro SD, Mazzarotto P, Gioffre G and Speciale G. Identifying factors that predict the choice and success rate of radial artery catheterisation in contemporary real world cardiology practice: a sub-analysis of the PREVAIL study data. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2010;6:240-6.
145. Kiemeneij F, Vajifdar BU, Eccleshall SC, Laarman G, Slagboom T and van der Wieken R. Evaluation of a spasmolytic cocktail to prevent radial artery spasm during coronary procedures. *Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions*. 2003;58:281-4.
146. Ball WT, Sharieff W, Jolly SS, Hong T, Kutryk MJ, Graham JJ, Fam NP, Chisholm RJ and Cheema AN. Characterization of operator learning curve for transradial coronary interventions. *Circ Cardiovasc Interv*. 2011;4:336-41.
147. Kotowycz MA and Dzavik V. Radial artery patency after transradial catheterization. *Circ Cardiovasc Interv*. 2012;5:127-33.
148. Jolly SS, Amlani S, Hamon M, Yusuf S and Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J*. 2009;157:132-40.
149. Agostoni P, Biondi-Zoccai GG, de Benedictis ML, Rigattieri S, Turri M, Anselmi M, Vassanelli C, Zardini P, Louvard Y and Hamon M. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures; Systematic overview and meta-analysis of randomized trials. *Journal of the American College of Cardiology*. 2004;44:349-56.
150. Verheugt FW, Steinhubl SR, Hamon M, Darius H, Steg PG, Valgimigli M, Marso SP, Rao SV, Gershlick AH, Lincoff AM, Mehran R and Stone GW. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2011;4:191-7.
151. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, Moretti C, Agostoni P, Loschiavo P, Lioy E, Sheiban I and Sangiorgi G. Radial versus femoral randomized investigation in ST-segment elevation acute

coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *Journal of the American College of Cardiology*. 2012;60:2481-9.
152. Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, Rubartelli P, Briguori C, Andò G, Repetto A, Limbruno U, Cortese B, Sganzerla P, Lupi A, Galli M, Colangelo S, Ierna S, Ausiello A, Presbitero P, Sardella G, Varbella F, Esposito G, Santarelli A, Tresoldi S, Nazzaro M, Zingarelli A, de Cesare N, Rigattieri S, Tosi P, Palmieri C, Brugaletta S, Rao SV, Heg D, Rothenbühler M, Vranckx P and Jüni P. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *The Lancet*. 2015;385:2465-2476.
153. Ferrante G, Rao SV, Juni P, Da Costa BR, Reimers B, Condorelli G, Anzuini A, Jolly SS, Bertrand OF, Krucoff MW, Windecker S and Valgimigli M. Radial Versus Femoral Access for Coronary Interventions Across the Entire Spectrum of Patients With Coronary Artery Disease: A Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv*. 2016;9:1419-34.
154. Kolkailah AA, Alreshq RS, Muhammed AM, Zahran ME, Anas El-Wegoud M and Nabhan AF. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. *The Cochrane database of systematic reviews*. 2018;4:Cd012318.
155. Barbato E, Dudek D, Baumbach A, Windecker S and Haude M. Current trends in coronary interventions: an overview from the EAPCI registries. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2017;13:Z8-Z10.
156. Serrador Frutos AM, Jimenez-Quevedo P, Perez de Prado A and Pan Alvarez-Ossorio M. Spanish Cardiac Catheterization and Coronary Intervention Registry. 26th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2016). *Rev Esp Cardiol (Engl Ed)*. 2017;70:1110-1120.
157. Biswas S, Duffy SJ, Lefkovits J, Andrianopoulos N, Brennan A, Walton A, Chan W, Noaman S, Shaw JA, Dawson L, Ajani A, Clark DJ, Freeman M, Hiew C, Oqueli E, Reid CM and Stub D. Australian Trends in Procedural Characteristics and Outcomes in Patients Undergoing Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction. *Am J Cardiol*. 2018;121:279-288.
158. Rigattieri S, Valsecchi O, Sciahbasi A, Tomassini F, Limbruno U, Marchese A, La Manna A, Mauro C, Varbella F, Berti S, Tarantino FF and Musumeci G. Current practice of transradial approach for coronary procedures: A survey by the Italian Society of Interventional Cardiology (SICI-GISE) and the Italian Radial Club. *Cardiovasc Revasc Med*. 2017;18:154-159.
159. Johnman C, Pell JP, Mackay DF, Behan M, Slack R, Oldroyd KG and Berry C. Clinical outcomes following radial versus femoral artery access in primary or rescue percutaneous coronary intervention in Scotland: retrospective cohort study of 4534 patients. *Heart (British Cardiac Society)*. 2012;98:552-7.
160. Mamas MA, Nolan J, de Belder MA, Zaman A, Kinnaird T, Curzen N, Kwok CS, Buchan I, Ludman P, Kontopantelis E, British Cardiovascular Intervention S and the National Institute for Clinical Outcomes R. Changes in Arterial Access Site and Association With Mortality in the United Kingdom: Observations From a National Percutaneous Coronary Intervention Database. *Circulation*. 2016;133:1655-67.
161. Anderson HV. Transradial Access for Primary Percutaneous Coronary Intervention: Catching On and Catching Up. *JACC Cardiovasc Interv*. 2017;10:2255-2257.

162. Eleid MF, Rihal CS, Gulati R and Bell MR. Systematic use of transradial PCI in patients with ST-segment elevation myocardial infarction: a call to "arms". *JACC Cardiovasc Interv*. 2013;6:1145-8.
163. Shah R and Ahmed AJ. Validity of Randomized Trials Comparing Radial Versus Femoral Access in Acute Coronary Syndrome. *JACC Cardiovasc Interv*. 2016;9:1517-8.
164. Valle JA, Kaltenbach LA, Bradley SM, Yeh RW, Rao SV, Gurm HS, Armstrong EJ, Messenger JC and Waldo SW. Variation in the Adoption of Transradial Access for ST-Segment Elevation Myocardial Infarction: Insights From the NCDR CathPCI Registry. *JACC Cardiovasc Interv*. 2017;10:2242-2254.
165. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U and Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart (British Cardiac Society)*. 2010;96:1617-21.
166. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, Stephansson O and Ye W. Registers of the Swedish total population and their use in medical research. *European journal of epidemiology*. 2016;31:125-36.
167. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet (London, England)*. 2005;365:82-93.
168. Jones DS and Podolsky SH. The history and fate of the gold standard. *Lancet (London, England)*. 2015;385:1502-3.
169. Rosenberg W and Donald A. Evidence based medicine: an approach to clinical problem-solving. *BMJ (Clinical research ed)*. 1995;310:1122-6.
170. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB and Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ (Clinical research ed)*. 1996;312:71-72.
171. Frieden TR. Evidence for Health Decision Making - Beyond Randomized, Controlled Trials. *The New England journal of medicine*. 2017;377:465-475.
172. Bothwell LE, Greene JA, Podolsky SH and Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. *The New England journal of medicine*. 2016;374:2175-81.
173. STREPTOMYCIN treatment of pulmonary tuberculosis. *British medical journal*. 1948;2:769-82.
174. Crofton J. The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line. *Journal of the Royal Society of Medicine*. 2006;99:531-4.
175. Stanley K. Design of randomized controlled trials. *Circulation*. 2007;115:1164-9.
176. Altman DG and Dore CJ. Randomisation and baseline comparisons in clinical trials. *Lancet (London, England)*. 1990;335:149-53.
177. Rothman KJ. *Epidemiology : an introduction*. New York: Oxford University Press; 2012.
178. Motulsky HJ. *Intuitive biostatistics : a nonmathematical guide to statistical thinking*. [S.l.]: [s.n.]; 2014.
179. Rothman KJ. Causes. *American journal of epidemiology*. 1976;104:587-92.
180. Mamdani M, Sykora K, Li P, Normand SL, Streiner DL, Austin PC, Rochon PA and Anderson GM. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ (Clinical research ed)*. 2005;330:960-2.
181. Hill AB. Reflections on controlled trial. *Annals of the rheumatic diseases*. 1966;25:107-13.
182. Horton R. Common sense and figures: the rhetoric of validity in medicine (Bradford Hill Memorial Lecture 1999). *Statistics in medicine*. 2000;19:3149-64.

183. Silverman SL. From randomized controlled trials to observational studies. *The American journal of medicine*. 2009;122:114-20.
184. Nallamothu BK, Hayward RA and Bates ER. Beyond the randomized clinical trial: the role of effectiveness studies in evaluating cardiovascular therapies. *Circulation*. 2008;118:1294-303.
185. McKnight PE. *Missing data : a gentle introduction*. New York: Guilford Press; 2007.
186. Chavez-MacGregor M and Giordano SH. Randomized Clinical Trials and Observational Studies: Is There a Battle? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2016;34:772-3.
187. Britton A, McKee M, Black N, McPherson K, Sanderson C and Bain C. Threats to applicability of randomised trials: exclusions and selective participation. *Journal of health services research & policy*. 1999;4:112-21.
188. Motheral BR and Fairman KA. The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clinical therapeutics*. 1997;19:346-66.
189. Britton A, McKee M, Black N, McPherson K, Sanderson C and Bain C. Choosing between randomised and non-randomised studies: a systematic review. *Health technology assessment (Winchester, England)*. 1998;2:i-iv, 1-124.
190. Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, Lam M and Seguin R. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC medical research methodology*. 2003;3:28.
191. Newhouse JP and McClellan M. Econometrics in outcomes research: the use of instrumental variables. *Annual review of public health*. 1998;19:17-34.
192. Dworeck C. Did you really read this? Allow me to invite you to coffee and princesstårta (if you are one of the first 5). . *Int J Coffeelogy*. 2019:01.
193. Smith GD and Egger M. Incommunicable knowledge? Interpreting and applying the results of clinical trials and meta-analyses. *Journal of clinical epidemiology*. 1998;51:289-95.
194. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ (Clinical research ed)*. 1996;312:1215-8.
195. Col NF, Gurwitz JH, Alpert JS and Goldberg RJ. Frequency of inclusion of patients with cardiogenic shock in trials of thrombolytic therapy. *Am J Cardiol*. 1994;73:149-57.
196. Vlahakes GJ. The value of phase 4 clinical testing. *The New England journal of medicine*. 2006;354:413-5.
197. Ioannidis JP and Lau J. The impact of high-risk patients on the results of clinical trials. *Journal of clinical epidemiology*. 1997;50:1089-98.
198. Califf RM, Pryor DB and Greenfield JC, Jr. Beyond randomized clinical trials: applying clinical experience in the treatment of patients with coronary artery disease. *Circulation*. 1986;74:1191-4.
199. McKee M, Britton A, Black N, McPherson K, Sanderson C and Bain C. Methods in health services research. Interpreting the evidence: choosing between randomised and non-randomised studies. *BMJ (Clinical research ed)*. 1999;319:312-5.
200. Sorensen HT, Lash TL and Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology (Baltimore, Md)*. 2006;44:1075-82.
201. Stukenborg GJ. Comparison of carotid endarterectomy outcomes from randomized controlled trials and Medicare administrative databases. *Archives of neurology*. 1997;54:826-32.
202. Buks E, Schuster R, Heiblum M, Mahalu D and Umansky V. Dephasing in electron interference by a 'which-path' detector. *Nature*. 1998;391:871.

203. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM and Platt R. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? *The New England journal of medicine*. 1995;332:1125-31.
204. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *The New England journal of medicine*. 1989;321:406-12.
205. Kereiakes DJ, Teirstein PS, Sarembock IJ, Holmes DR, Jr., Krucoff MW, O'Neill WW, Waksman R, Williams DO, Popma JJ, Buchbinder M, Mehran R, Meredith IT, Moses JW and Stone GW. The truth and consequences of the COURAGE trial. *Journal of the American College of Cardiology*. 2007;50:1598-603.
206. Bourgeois FT, Murthy S and Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med*. 2010;153:158-66.
207. Bodenheimer T. Uneasy alliance--clinical investigators and the pharmaceutical industry. *The New England journal of medicine*. 2000;342:1539-44.
208. James S, Rao SV and Granger CB. Registry-based randomized clinical trials--a new clinical trial paradigm. *Nature reviews Cardiology*. 2015;12:312-6.
209. Lauer MS and D'Agostino RB, Sr. The randomized registry trial--the next disruptive technology in clinical research? *The New England journal of medicine*. 2013;369:1579-81.
210. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angeras O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Karegren A, Nilsson J, Robertson L, Sandhall L, Sjogren I, Ostlund O, Harnek J and James SK. Thrombus aspiration during ST-segment elevation myocardial infarction. *The New England journal of medicine*. 2013;369:1587-97.
211. Erlinge D, Omerovic E, Frobert O, Linder R, Danielewicz M, Hamid M, Swahn E, Henareh L, Wagner H, Hardhammar P, Sjogren I, Stewart J, Grimfjard P, Jensen J, Aasa M, Robertsson L, Lindroos P, Haupt J, Wikstrom H, Ulvenstam A, Bhiladvala P, Lindvall B, Lundin A, Todt T, Ioanes D, Ramunddal T, Kellerth T, Zagozdzon L, Gotberg M, Andersson J, Angeras O, Ostlund O, Lagerqvist B, Held C, Wallentin L, Schersten F, Eriksson P, Koul S and James S. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. *The New England journal of medicine*. 2017;377:1132-1142.
212. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. *The Journal of thoracic and cardiovascular surgery*. 2007;134:1128-35.
213. Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, Colthart IR, Ross S, Shepherd SM and Russell D. Factors that limit the quality, number and progress of randomised controlled trials. *Health technology assessment (Winchester, England)*. 1999;3:1-143.
214. Boutron I, Altman DG, Moher D, Schulz KF and Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med*. 2017;167:40-47.
215. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA and Schneeweiss S. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *Journal of clinical epidemiology*. 2009;62:1226-32.
216. Mega JL, Braunwald E, Wiviott SD, Bassand J-P, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KAA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FWA and Gibson CM. Rivaroxaban in Patients with a Recent Acute Coronary Syndrome. *New England Journal of Medicine*. 2012;366:9-19.

217. Krantz MJ and Kaul S. The ATLAS ACS 2-TIMI 51 trial and the burden of missing data: (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2-Thrombolysis In Myocardial Infarction 51). *Journal of the American College of Cardiology*. 2013;62:777-81.
218. Black N. High-quality clinical databases: breaking down barriers. *Lancet (London, England)*. 1999;353:1205-6.
219. Faraoni D and Schaefer ST. Randomized controlled trials vs. observational studies: why not just live together? *BMC Anesthesiology*. 2016;16:102.
220. Trentino K, Farmer S, Gross I, Shander A and Isbister J. Observational studies - should we simply ignore them in assessing transfusion outcomes? *BMC Anesthesiol*. 2016;16:96.
221. Smith GCS and Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ (Clinical research ed)*. 2003;327:1459-1461.
222. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K and Ray WA. Major congenital malformations after first-trimester exposure to ACE inhibitors. *The New England journal of medicine*. 2006;354:2443-51.
223. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K and Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *The New England journal of medicine*. 2004;351:1089-96.
224. Schneeweiss S and Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *Journal of clinical epidemiology*. 2005;58:323-37.
225. Angus DC. Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems? *Jama*. 2015;314:767-8.
226. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Statistics in medicine*. 2014;33:1242-58.
227. Lobo FS, Wagner S, Gross CR and Schommer JC. Addressing the issue of channeling bias in observational studies with propensity scores analysis. *Research in social & administrative pharmacy : RSAP*. 2006;2:143-51.
228. Austin PC and Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Statistics in medicine*. 2006;25:2084-106.
229. Benson K and Hartz AJ. A comparison of observational studies and randomized, controlled trials. *The New England journal of medicine*. 2000;342:1878-86.
230. Concato J, Shah N and Horwitz RI. Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs. *New England Journal of Medicine*. 2000;342:1887-1892.
231. Papanikolaou PN, Christidi GD and Ioannidis JP. Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2006;174:635-41.
232. Kunz R and Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ (Clinical research ed)*. 1998;317:1185-90.
233. Schneeweiss S, Patrick AR, Sturmer T, Brookhart MA, Avorn J, Maclure M, Rothman KJ and Glynn RJ. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Medical care*. 2007;45:S131-42.

234. von Elm E, Altman DG, Egger M and et al. The strengthening the reporting of observational studies in epidemiology (strobe) statement: Guidelines for reporting observational studies. *Annals of Internal Medicine*. 2007;147:573-577.
235. Dreyer NA, Schneeweiss S, McNeil BJ, Berger ML, Walker AM, Ollendorf DA and Gliklich RE. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. *The American journal of managed care*. 2010;16:467-71.
236. Glaeser EL. Researcher incentives and empirical methods. . *Harvard Institute of Economic*

Research Discussion Paper No 2122. 2006.
237. Young SS and Karr A. Deming, data and observational studies: A process out of control and needing fixing. *Significance Significance*. 2011;8:116-120.
238. Phillips CV. Publication bias in situ. *BMC medical research methodology*. 2004;4:20.
239. Lovell MC. Data Mining. *The Review of Economics and Statistics*. 1983;65:1-12.
240. http://www.jerrydallal.com/lhsp/multtest.htm.
241. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. *Statistics in medicine*. 2007;26:20-36.
242. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf.
243. Young SS and Yu M. Association of bisphenol A with diabetes and other abnormalities. *Jama*. 2009;301:720-1; author reply 721-2.
244. Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *Proceedings of the Royal Society of Medicine*. 1965;58:295-300.
245. Thygesen LC, Andersen GS and Andersen H. A philosophical analysis of the Hill criteria. *Journal of epidemiology and community health*. 2005;59:512-6.
246. Susser M. What is a Cause and How Do We Know One? A Grammar for Pragmatic Epidemiology. *American journal of epidemiology*. 1991;133:635-648.
247. Lucas RM and McMichael AJ. Association or causation: evaluating links between "environment and disease". *Bulletin of the World Health Organization*. 2005;83:792-5.
248. Okasha S. *Philosophy of science : a very short introduction*. Oxford: Oxford University Press; 2016.
249. Popper K. *Popper : the logic of scientific discovery*. London: Routledge Classics; 2002.
250. United S, Surgeon General's Advisory Committee on S and Health. *Smoking and health; report of the advisory committee to the Surgeon General of the Public Health Service*. [Washington: U.S. Dept. of Health, Education, and Welfare, Public Health Service; [for sale by the Superintendent of Documents, U.S. Govt. Print. Off.]; 1964.
251. Doll R and Hill AB. Smoking and carcinoma of the lung; preliminary report. *British medical journal*. 1950;2:739-48.
252. Cornfield J, Haenszel W, Hammond EC, Lilienfeld AM, Shimkin MB and Wynder EL. Smoking and lung cancer: recent evidence and a discussion of some questions. *Journal of the National Cancer Institute*. 1959;22:173-203.
253. SMOKING and health; joint report of the Study Group on Smoking and Health. *Science (New York, NY)*. 1957;125:1129-33.
254. Ioannidis JP. Exposure-wide epidemiology: revisiting Bradford Hill. *Statistics in medicine*. 2016;35:1749-62.

255. Hofler M. The Bradford Hill considerations on causality: a counterfactual perspective. *Emerging themes in epidemiology*. 2005;2:11.
256. Phillips CV and Goodman KJ. The missed lessons of Sir Austin Bradford Hill. *Epidemiologic perspectives & innovations : EP+I*. 2004;1:3.
257. Fedak KM, Bernal A, Capshaw ZA and Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerging themes in epidemiology*. 2015;12:14.
258. Irving M, Eramudugolla R, Cherbuin N and Anstey KJ. A Critical Review of Grading Systems: Implications for Public Health Policy. *Evaluation & the health professions*. 2017;40:244-262.
259. Feinstein AR and Horwitz RI. Double standards, scientific methods, and epidemiologic research. *The New England journal of medicine*. 1982;307:1611-7.
260. Goodman S. A dirty dozen: twelve p-value misconceptions. *Seminars in hematology*. 2008;45:135-40.
261. Lang JM, Rothman KJ and Cann CI. That confounded P-value. *Epidemiology (Cambridge, Mass)*. 1998;9:7-8.
262. Greenland S. Bayesian interpretation and analysis of research results. *Seminars in hematology*. 2008;45:141-9.
263. Ioannidis JP. Why most published research findings are false. *PLoS medicine*. 2005;2:e124.
264. Sullivan GM and Feinn R. Using Effect Size-or Why the P Value Is Not Enough. *Journal of graduate medical education*. 2012;4:279-82.
265. Observation of a new boson at a mass of 125 GeV with the CMS experiment at the LHC.
266. Baser O. Too much ado about propensity score models? Comparing methods of propensity score matching. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2006;9:377-85.
267. Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41-55.
268. Kuss O, Blettner M and Borgermann J. Propensity Score: an Alternative Method of Analyzing Treatment Effects. *Deutsches Arzteblatt international*. 2016;113:597-603.
269. Stuart EA, Marcus SM, Horvitz-Lennon MV, Gibbons RD and Normand SL. Using Non-experimental Data to Estimate Treatment Effects. *Psychiatric annals*. 2009;39:41451.
270. Cepeda MS, Boston R, Farrar JT and Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *American journal of epidemiology*. 2003;158:280-7.
271. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ and Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *Jama*. 2007;297:278-85.
272. Peduzzi P, Concato J, Kemper E, Holford TR and Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of clinical epidemiology*. 1996;49:1373-9.
273. Imai K, King G and Stuart EA. Misunderstandings between experimentalists and observationalists about causal inference. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*. 2008;171:481-502.

274. Morgan CJ. Reducing bias using propensity score matching. *Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology*. 2018;25:404-406.
275. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA and Schneeweiss S. Instrumental variables II: instrumental variable application-in 25 variations, the physician prescribing preference generally was strong and reduced covariate imbalance. *Journal of clinical epidemiology*. 2009;62:1233-41.
276. Hernan MA and Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology (Cambridge, Mass)*. 2006;17:360-72.
277. Martens EP, Pestman WR, de Boer A, Belitser SV and Klungel OH. Instrumental variables: application and limitations. *Epidemiology (Cambridge, Mass)*. 2006;17:260-7.
278. Harris KM and Remler DK. Who is the marginal patient? Understanding instrumental variables estimates of treatment effects. *Health services research*. 1998;33:1337-60.
279. Brookhart MA, Rassen JA and Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. *Pharmacoepidemiology and drug safety*. 2010;19:537-54.
280. Greenland S. An introduction To instrumental variables for epidemiologists. *International journal of epidemiology*. 2000;29:1102.
281. Ertefaie A, Small DS, Flory JH and Hennessy S. A tutorial on the use of instrumental variables in pharmacoepidemiology. *Pharmacoepidemiology and drug safety*. 2017;26:357-367.
282. Bound J, Jaeger DA and Baker RM. Problems with Instrumental Variables Estimation When the Correlation Between the Instruments and the Endogeneous Explanatory Variable is Weak. *Journal of the American Statistical Association*. 1995;90:443-450.
283. Vertosick EA, Assel M and Vickers AJ. A systematic review of instrumental variable analyses using geographic region as an instrument. *Cancer epidemiology*. 2017;51:49-55.
284. Rassen JA, Schneeweiss S, Glynn RJ, Mittleman MA and Brookhart MA. Instrumental variable analysis for estimation of treatment effects with dichotomous outcomes. *American journal of epidemiology*. 2009;169:273-84.
285. Kawachi I and Berkman LF. *Neighborhoods and health*. New York; Oxford: Oxford University Press; 2003.
286. Diez Roux AV. Investigating neighborhood and area effects on health. *American journal of public health*. 2001;91:1783-9.
287. Diez-Roux AV. Multilevel analysis in public health research. *Annual review of public health*. 2000;21:171-92.
288. Larsen K and Merlo J. Appropriate assessment of neighborhood effects on individual health: integrating random and fixed effects in multilevel logistic regression. *American journal of epidemiology*. 2005;161:81-8.
289. Snijders TAB and Bosker RJ. *Multilevel analysis : an introduction to basic and advanced multilevel modeling*. London; Thousand Oaks, Calif.: Sage Publications; 2002.
290. Sanagou M, Wolfe R, Forbes A and Reid CM. Hospital-level associations with 30-day patient mortality after cardiac surgery: a tutorial on the application and interpretation of marginal and multilevel logistic regression. *BMC medical research methodology*. 2012;12:28.
291. Larsen K, Petersen JH, Budtz-Jorgensen E and Endahl L. Interpreting parameters in the logistic regression model with random effects. *Biometrics*. 2000;56:909-14.
292. Newgard CD and Lewis RJ. Missing Data: How to Best Account for What Is Not Known. *Jama*. 2015;314:940-1.
293. Rubin DB. Inference and Missing Data. *Biometrika*. 1976;63:581-592.

294. Perkins NJ, Cole SR, Harel O, Tchetgen Tchetgen EJ, Sun B, Mitchell EM and Schisterman EF. Principled Approaches to Missing Data in Epidemiologic Studies. *American journal of epidemiology*. 2018;187:568-575.
295. He Y. Missing data analysis using multiple imputation: getting to the heart of the matter. *Circulation Cardiovascular quality and outcomes*. 2010;3:98-105.
296. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM and Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ (Clinical research ed)*. 2009;338:b2393.
297. Scheuren F. Multiple Imputation: How It Began and Continues. *The American Statistician*. 2005;59:315-319.
298. Rubin DB. The Design of a General and Flexible System for Handling Nonresponse in Sample Surveys. *The American Statistician*. 2004;58:298-302.
299. Harel O, Mitchell EM, Perkins NJ, Cole SR, Tchetgen Tchetgen EJ, Sun B and Schisterman EF. Multiple Imputation for Incomplete Data in Epidemiologic Studies. *American journal of epidemiology*. 2018;187:576-584.
300. Li P, Stuart EA and Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. *Jama*. 2015;314:1966-7.
301. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical methods in medical research*. 2007;16:219-42.
302. Sargan JD. The Estimation of Economic Relationships using Instrumental Variables. *Econometrica*. 1958;26:393-415.
303. Ando G, Cortese B, Russo F, Rothenbuhler M, Frigoli E, Gargiulo G, Briguori C, Vranckx P, Leonardi S, Guiducci V, Belloni F, Ferrari F, de la Torre Hernandez JM, Curello S, Liistro F, Perkan A, De Servi S, Casu G, Dellavalle A, Fischetti D, Micari A, Loi B, Mangiacapra F, Russo N, Tarantino F, Saia F, Heg D, Windecker S, Juni P, Valgimigli M and Investigators M. Acute Kidney Injury After Radial or Femoral Access for Invasive Acute Coronary Syndrome Management: AKI-MATRIX. *Journal of the American College of Cardiology*. 2017.
304. Cortese B, Sciahbasi A, Sebik R, Rigattieri S, Alonzo A, Silva-Orrego P, Belloni F, Seregni RG, Giovannelli F, Tespili M, Ricci R and Berni A. Comparison of risk of acute kidney injury after primary percutaneous coronary interventions with the transradial approach versus the transfemoral approach (from the PRIPITENA urban registry). *Am J Cardiol*. 2014;114:820-5.
305. Ando G, Costa F, Trio O, Oreto G and Valgimigli M. Impact of vascular access on acute kidney injury after percutaneous coronary intervention. *Cardiovasc Revasc Med*. 2016;17:333-8.
306. Kooiman J, Seth M, Nallamothu BK, Heung M, Humes D and Gurm HS. Association between acute kidney injury and in-hospital mortality in patients undergoing percutaneous coronary interventions. *Circ Cardiovasc Interv*. 2015;8:e002212.
307. Jolly SS, Niemela K, Xavier D, Widimsky P, Budaj A, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Cairns J, Chrolavicius S, Yusuf S and Mehta SR. Design and rationale of the radial versus femoral access for coronary intervention (RIVAL) trial: a randomized comparison of radial versus femoral access for coronary angiography or intervention in patients with acute coronary syndromes. *Am Heart J*. 2011;161:254-260 e1-4.
308. Doyle BJ, Rihal CS, Gastineau DA and Holmes DR, Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *Journal of the American College of Cardiology*. 2009;53:2019-27.

309. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS and Califf RM. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *Jama*. 2004;292:1555-62.
310. Smith KJ, Bleyer AJ, Little WC and Sane DC. The cardiovascular effects of erythropoietin. *Cardiovascular research*. 2003;59:538-48.
311. Corwin HL, Gettinger A, Fabian TC, May A, Pearl RG, Heard S, An R, Bowers PJ, Burton P, Klausner MA and Corwin MJ. Efficacy and safety of epoetin alfa in critically ill patients. *The New England journal of medicine*. 2007;357:965-76.
312. Thiele H, Allam B, Chatellier G, Schuler G and Lafont A. Shock in acute myocardial infarction: the Cape Horn for trials? *European heart journal*. 2010;31:1828-35.
313. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB and Cohen MG. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation*. 2017;136:e232-e268.
314. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV, Jr., Peterson ED and Alexander KP. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009;119:1873-82.
315. Boden H, Velders MA, van der Hoeven BL, Cannegieter SC and Schalij MJ. In-hospital major bleeding and its clinical relevance in patients with ST elevation myocardial infarction treated with primary percutaneous coronary intervention. *Am J Cardiol*. 2013;112:1533-9.