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Percutaneous Coronary and Structural Interventions in Women

A Position Statement from the EAPCI Women Committee

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Short Running Title: EAPCI Women Committee Position Statement

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Abbreviations

ACS=Acute Coronary Syndrome

BMS=Bare Metal Stent

BVS=Bioresorbable Vascular Scaffold

CABG=Coronary Artery Bypass Grafting

CAD=Coronary Artery Disease

CTO=Chronic Total Occlusion

CVA=Cerebrovascular Accident

DES=Drug-eluting Stent

EAPCI=European Association Percutaneous Coronary Intervention

ECG=Electrocardiogram

EES=Everolimus-Eluting Stent

HR=Hazard Ratio

LAA=Left Atrial Appendage

LVEF=Left Ventricular Ejection Fraction

MACE=Major Adverse Cardiovascular Events

MR=Mitral Regurgitation

PCI=Percutaneous Coronary Intervention

RR=Relative Risk

SAVR=Surgical Aortic Valve Replacement

STEMI=ST Elevation Myocardial Infarction

TAVI=Transcatheter Aortic Valve Implantation

TR=Tricuspid Regurgitation

ULMCA=Unprotected Left Main Coronary Artery

VARC=Valve Academic Research Consortium

Abstract

Several expert documents on sex-based differences in interventional outcomes are now available, however this is the first position paper from the EAPCI Women Committee discussing the potential influence of sex in the percutaneous treatment of coronary and structural heart disease

Despite the misconception that coronary artery disease is a 'man's disease', contemporary data shows a growing incidence in women. However, women are under-represented in randomized coronary clinical trials (~25%). The generalization of such studies is therefore problematic in decision-making for females undergoing coronary intervention. Differences in pathophysiology between sexes exist, highlighting the need for greater awareness amongst healthcare professionals to enable best evidence-based therapies for women as well as for men.

Reassuringly, women represent half of the population included in transcatheter aortic valve implantation clinical trials and may actually benefit more. Growing evidence is also emerging for other interventional atrial procedures which may well be advantageous to women.

Awareness of sex disparities is increasing, and we must all work collaboratively within our profession to ensure we provide effective care for all patients with heart disease. The EAPCI Women Committee aim to highlight such issues through this position paper and through visibility within the interventional community.

Introduction

Despite the common misconception that coronary artery disease (CAD) is a 'man's disease', some contemporary data shows a growing incidence of CAD across Europe in women[1]. However, women are usually under-represented in randomized coronary clinical trials, accounting for ~25% of patients, with contributing factors being co-morbidities, child-bearing potential and older age. This makes the generalization of such studies problematic in decision-making for individual females undergoing percutaneous coronary intervention (PCI). Registry data show that despite having smaller vessels than men, women are less likely to receive drug-eluting stents (DES)[2]. The prevalence of risk factors for stent thrombosis and restenosis, including older age, diabetes mellitus, and small vessel size, is also different between sexes undergoing PCI, which raises the important question concerning whether patient sex modifies significantly the relationship between stent type and PCI outcomes during long-term follow-up[3, 4]. Table 1 reports current knowledge gaps in this area. As opposed to studies of CAD, women represent half of the population included in clinical trials evaluating transcatheter aortic valve implantation (TAVI) for the treatment of symptomatic aortic stenosis. Figure 1 shows a diagrammatic representation of the impact of both CAD and structural heart disease upon women and the comparable results of subsequent intervention with men.

On this background, the EAPCI Women Committee met during the European Society of Cardiology Congress on 26th August 2017 in Barcelona, Spain, with the aim to develop a position paper regarding the potential influence of sex in the percutaneous treatment of both CAD and structural heart disease. This extends upon prior published expert documents on sex-based differences in interventional outcomes.

Pathophysiology of Coronary Artery and Structural Heart Disease in Women

Coronary Artery Disease

Almost 70% of women presenting with stable angina have been reported to have non-obstructive CAD (NOCAD)[5]. Microvascular Coronary Dysfunction (MCD) has been demonstrated to be the main mechanism of angina in women ≤65 years of age. The definitive diagnosis can be assessed with the use of invasive coronary vasomotor testing or consideration of positron emission tomography scanning and should not be underestimated due to the worse prognosis of MCD[6]. Intravascular imaging and functional assessment can be used for further assessment, as discussed later. Another mechanism to be considered is that women more often have hypertrophy of the left ventricle and in the setting of relative anemia, there may be a mismatch in the oxygen supply and demand.

Acute Coronary Syndromes

Another important difference in acute coronary syndrome (ACS) pathophysiology between men and women is that, similar to stable angina, women are more likely to have NOCAD on angiography. There are many potential explanations for this, such as angiographic underestimation of the true CAD burden, higher-risk plaque characteristics, MCD, spontaneous coronary artery dissection (SCAD), coronary spasm or Takotsubo cardiomyopathy. Women presenting with ACS, more frequently non-STEMI than men, with NOCAD have an elevated risk of cardiac events[7], suggesting that appropriate diagnosis and optimal secondary prevention with anti-platelet agents and statins are essential.

Spontaneous Coronary Artery Dissection

The spontaneous separation of the layers of the coronary artery wall, termed SCAD, notably being neither iatrogenic nor traumatic, is gaining recognition as an important cause of ACS especially in young women. Indeed, in contemporary series, women accounted for 92-95% of the population with SCAD (mean age 44-55 years) with a prevalence of 22-43% in young women, higher among those with pregnancy-related myocardial infarction (MI)[8]. Coronary angiography is the first-line

imaging modality for these patients; however, it has significant limitations as only the lumen and not the arterial wall is visualized, with only one third obvious by angiography alone. Therefore, dedicated intracoronary imaging techniques may improve diagnosis.

Takotsubo Cardiomyopathy

Another presentation of ACS, more common in women (9:1), is Takotsubo cardiomyopathy which is associated with an early mortality of 3–5% and is the cause of MI in 1-8% of women[9]. This syndrome is typically, but not always, caused by emotional stress, with catecholamine release leading to stunning of the myocardium with hypokinesia/akinesia in the mid-segments and apex of the left ventricle. To date, there is no specific therapy, but recommended strategies aim to prevent cardiogenic shock/arrhythmias, avoiding catecholamine release.

Structural Heart Disease

At the time of treatment, women with aortic stenosis are approximately 2 years older compared to their male counterparts, with typically higher transvalvular pressure gradients and smaller valve areas[10].

Furthermore, the left ventricular response to increased afterload in aortic stenosis shows sex specific differences with concentric hypertrophy, smaller left ventricular volumes and preserved left ventricular ejection fraction in women, whereas men more often develop left ventricular dilatation, fibrosis and systolic dysfunction[11]. The typical left ventricular geometry in women also contributes to the higher prevalence of paradoxical low-flow low-gradient AS.

Several sex differences have been observed in mitral valve pathology and mitral regurgitation characteristics in patients undergoing mitral valve surgery. Posterior leaflet prolapse, flail and annular dilatation are more frequent in men, who are more likely to require surgery. In contrast, mitral annular

calcification, leaflet thickening and myxomatous mitral valves and the presence of some degree of mitral stenosis are more common in women[12].

Intra Coronary Imaging Modalities and Functional Assessment in Women

Coronary Plaque Morphology

Several studies using intravascular ultrasound (IVUS) have demonstrated that women have a lower atherosclerotic plaque burden[13]. Regarding plaque composition, studies have shown some differences in calcium and necrotic core components that tend to be attenuated in older and stable patients[14].

Intracoronary imaging has confirmed in vivo the sex differences in the substrate for ACS, especially in young women. A recent IVUS study demonstrated that in ST elevation myocardial infarction (STEMI) patients <65 years old, 59% of men versus 22% of women had plaque rupture. In those ≥65 years, no differences in culprit plaque morphology were found[15]. High-resolution intracoronary imaging with OCT has been able to demonstrate in vivo the presence of plaque erosion[16]. Furthermore, IVUS and especially OCT have also significantly contributed to increase the recognition of SCAD. Supplementary Figure 1 illustrates a case of a 51-year-old lady presenting with anterolateral STEMI with SCAD.

Functional Coronary Stenosis Severity Assessment

A number of studies have demonstrated that for similar degrees of coronary luminal obstruction, the fractional flow reserve (FFR) result is significantly higher in women compared with men. A sub-study of the landmark 'Fractional flow reserve versus Angiography for Multi-vessel Evaluation' (FAME) trial reported such results with angiographically equivalent lesions less likely to cause ischemia in women, with the proportion of FFR values ≤0.80 in 50-70% lesions lower in women than men (21.1% vs. 39.5%; p<0.001), however there was a similar relative risk reduction in death, MI and repeat revascularization with the use of FFR[17]. Indeed, when considering predicting FFR≤0.80,

IVUS had a lower positive predictive value in women, likely a consequence of the smaller body surface area and subsequent left ventricular mass and hence smaller myocardial territory at jeopardy[18]. The postulated reason for this finding is higher MCD in women and hence impaired response to vasodilators. If there remains doubt with regards to the significance of a lesion, then both FFR and IVUS should be utilized, assuming there are no issues with IVUS due to small vessel size.

Transcatheter Coronary and Structural Interventions in Women

Primary PCI

The significant benefits of early reperfusion in STEMI in both sexes are now unquestionable and this is reflected in current guidelines[19]. Nevertheless, women have a higher risk of in-hospital mortality and adverse outcomes including those in contemporary primary PCI studies[3, 20]. There are a number of reasons postulated which may contribute to inferior outcomes. Firstly, women delay longer seeking medical treatment for symptoms of STEMI[21]. There is also a demonstrable delay in door to balloon time[22]. In addition, women commonly have atypical symptoms including back or neck pain, pleuritic chest pain, indigestion and dyspnea[23]. STEMI may not be suspected initially, due to the unclear history and a general underestimation of the risk in women. One of the most important factors is the older age of women at presentation and co-morbidities. Women experience more bleeding complications, and it is recognized that significant bleeding is associated with a higher mortality[24]. Use of radial access, particularly in STEMI, has reduced this complication.

Complex Percutaneous Coronary Interventions

Women presenting with stable CAD and obstructive CAD frequently undergo complex PCI. Usually such patients are then excluded from randomized clinical trials. In the SYNTAX trial, women accounted for only 22.3% overall. Specifically, women with unprotected left main coronary artery (ULMCA) disease represented only 10.3%. When women from the ULMCA substudy were evaluated

(CABG n=85 and PCI n=100), there was no difference in the primary endpoint of major adverse cardiac and cerebrovascular events (MACE) (CABG 21.3% vs PCI 26.3%; p = 0.47) at 3 years. Furthermore, the SYNTAX II score revealed that females required lower anatomic SYNTAX scores to achieve similar mortality in both the PCI and CABG arms, as female sex is a clinical predictor in the model.

Limited available data comes also from retrospective data analysis, such as the Milan and New-Tokyo (MITO) Registry. In this challenging subset of patients with ULMCA disease, women had greater co-morbidities and more complex lesions, resulting in a higher incidence of cardiac death. After propensity matching, there was no difference in the occurrence of MACE but cardiac death showed only a trend to be higher in women[25]. As there were small numbers, this difference in cardiac events could be explained by the consideration that ULMCA disease in women may be influenced by those risk factors, not analyzed and considered in the propensity model.

The 'Interventional Cardiology Research In-cooperation Society-left MAIN revascularization' registry was recently published comparing 2,328 patients (23.4% women) undergoing ULMCA PCI with DES. At a median follow-up of 2.9 years (IQR 1.0-4.1) the incidence of all-cause death, MI or stroke was comparable between sexes (10.8% vs. 10.8%, log rank 0.587)[26]. A further sub-analysis from patient-level data from women enrolled in randomized DES trials focused on complex PCI showed an increased risk of MACE at 3 years in the complex PCI group, but use of new-generation DES did reduce MACE and stent thrombosis compared with first-generation devices[27]. With regards to chronic total occlusions (CTO), data from registries suggest that such complex PCI in women is safe and feasible. However, women are less likely to undergo percutaneous revascularization for a CTO and had a lower success rate following CTO procedure[28].

An example of complex PCI and concurrent TAVI of an elderly lady presenting with pulmonary edema and cardiogenic shock is illustrated in Supplementary Figure 2.

Impact of Coronary Stent Technologies Evolution

Under the auspices of the Society for Cardiovascular Angiography and Interventions' Women in Innovation Initiative (WIN), a patient-level meta-analysis has been undertaken to investigate the efficacy and safety profiles of DES in women[29]. A total of 11,557 women in 26 DES trials from 2000-2013 were included. At 3-years the estimated cumulative incidences of death or MI were 12.8%, 10.9% and 9.2% in female patients treated with BMS, first-generation DES and newer-generation DES, respectively (p=0.001). Corresponding rates of definite or probable stent thrombosis were 1.3%, 2.1% and 1.1%, respectively (p=0.01). The 3-year rate of target-lesion revascularization decreased significantly from 18.6% with BMS to 7.8% with first-generation DES and 6.3% with newer-generation DES (p<0.0001). These results were consistent after multivariable adjustment for potential confounding factors and in subgroup analyses. Overall, the results of this meta-analysis suggest that in women the use of DES compared with BMS is safe and effective and that newer-generation DES have further improved the safety and efficacy profile compared to early-generation DES[30]. This information provides reassurance regarding the performance of DES in women; however, the benefits must be weighed against the increased safety risk with dual antiplatelet therapy in subjects at risk of bleeding.

Transcatheter Aortic Valve Implantation

Multiple studies have shown that female sex is an independent predictor of worse outcomes after surgical aortic valve replacement (SAVR)[31] but is conversely potentially favourable in TAVI. The PARTNER trial demonstrated that amongst women, there was a trend for procedural mortality to be lower with TAVI versus SAVR (6.8% vs. 13.1%; p=0.07) and this finding was maintained throughout follow-up (HR 0.55; 95% CI 0.32-0.93; p=0.02)[32]. A recent meta-analysis of randomized clinical trials comparing TAVI versus SAVR, comprising 1,706 women, showed that TAVI patients had a substantial reduction in mortality (31% at 1-year and 26% at 2-years)[33]. The same meta-analysis also

suggested that females undergoing TAVI have lower peri-procedural mortality and lower rates of bleeding and acute kidney injury. Furthermore, there were lower procedural bleeding rates in women following TAVI than SAVR. Female sex is independently associated with better recovery of the left ventricular systolic function following TAVI[34]. A possible reason for this is that TAVI does not require the sewing ring to be present and hence there is a lower rate of severe prosthesis-patient mismatch (16%) compared with SAVR patients (29%) [35]. A large meta-analysis of 47,188 patients (49.4% women) undergoing TAVI confirmed a benefit favoring women in all-cause mortality at one-year (Relative Risk [RR] 0.85; 95% CI 0.79-0.91; p<0.001) with the survival advantage remaining consistent across multiple secondary analyses[36]. This is likely a consequence of less baseline co-morbidities, including less CAD prior to undergoing TAVI.

The WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry is the first all-female multi-national, prospective, observational registry of women undergoing TAVI for aortic stenosis. The purpose was to investigate the safety and performance of contemporary TAVI and to further explore the influence of female sex-specific factors which have never previously been investigated but may be relevant in the management. Women enrolled were intermediate to high-risk and experienced a 30-day Valve Academic Research Consortium (VARC)-2 composite safety endpoint of 14.0%. Age, prior stroke, LVEF <30%, TAVI device generation, and history of pregnancy were independent predictors of the 30-day composite safety endpoint[37]. The primary VARC-2 efficacy composite endpoint occurred in 111 (10.9%) patients beyond 30 days and in 167 (16.5%) patients at 1-year. The incidence of 1-year death or stroke was 13.9%. Prior coronary revascularization (HR: 1.72; 95% CI 1.17-2.52; p=0.006) indicating established CAD and EuroSCORE I (HR: 1.02; 95% CI 1.00-1.04; p=0.027) were independent predictors of the VARC-2 efficacy endpoint. Of note, after adjustment, no significant association was observed between history of pregnancy or any sex-specific factors and 1-year TAVR outcomes[38]. Finally, lower risk patients are now a matter of debate and several trials are ongoing. To date, TAVI in intermediate and high-

risk patients has been proven to be more successful in the female sex. Nevertheless, women at low risk may demonstrate the same trend.

Transcatheter Atrio-Ventricular Procedures - MitraClip

Sex-related differences in valve pathology, operative strategy, and long-term surgical outcome exist in mitral regurgitation (MR), but not in tricuspid regurgitation (TR)[39, 40]. In MR repair with MitraClip, implantation is safe and efficacious in both sexes[41], irrespective of baseline clinical and echocardiographic differences, despite a trend toward poorer functional improvement among women. Women less frequently receive ≥2 clips, and their mean post-intervention gradient is higher, probably due to lower body surface areas. For tricuspid clipping, the largest series (55% women) showed a 97% success rate, and good clinical results, without assessing sex differences[42]. No sex-specific guidelines exist for MitraClip; however current ESC guidelines state recommend edge-to-edge repair if the surgical risk is not low with, for primary MR, a ventricular dysfunction and a low likehood for surgical repair and, for secondary MR, an absence of need for surgical revascularization, with persisting symptoms despite optimal medical treatment[43].

Left Atrial Appendage Occlusion

As in coronary trials, women were under-represented in LAA occlusion trials (33%). Fewer hemorrhagic strokes and cardiovascular/unexplained deaths were observed with LAA occlusion compared to warfarin, with similar rates of stroke or systemic thromboembolism. Subgroup analyses did not show sex-related difference in efficacy and complication rate[44].

Indications for catheter-based LAA occlusion do not differ according to sex. Current ESC-guidelines recommend LAA occlusion for CHA_2DS_2-VASc score >2 while the EHRA/EAPCI expert consensus suggests extension to CHA_2DS_2-VASc score≥1[45]. Since female sex increases the CHA_2DS_2-VASc score by one point, women are more likely to fulfil the criteria for LAA occlusion.

Atrial Septal Defect Closure

Device closure has replaced surgery for secundum defect closure when morphologically feasible (80%) due to lower morbidity and shorter hospital stay, with similar success and mortality rates. Patients benefit from closure, at any age in terms of exercise capacity, dyspnea, and right heart failure, despite lower rhythmic benefit ≥40 years[46]. No data exists regarding the effect of patient sex. Device closure is preferred for secundum defect closure when applicable. It is particularly indicated in patients with significant shunt and pulmonary vascular resistance <5 WU regardless of symptoms, and in patients with paradoxical embolism[47].

Summary

This paper highlights the ongoing issues with the diagnosis and treatment of CAD in women. Differences in the pathophysiology between sexes are summarized, highlighting the need for a greater awareness amongst healthcare professionals to enable the best evidence-based therapies for women and men. Table 2 reports what could be done to improve outcomes in women.

Reassuringly, women are well represented in data concerning TAVI and may actually benefit more than men. Growing evidence is also emerging for other interventional atrial procedures which may well be advantageous to women.

Awareness of sex disparities is increasing, and we must all work collaboratively within our profession to ensure we provide timely and effective care for all patients with both CAD and structural heart disease in the future.

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Figure Legends

Figure 1. A diagrammatic representation of the impact of both CAD and structural heart disease upon women and the comparable results of subsequent intervention with men.

Tables.

Table 1. Current Knowledge Gaps in the Field

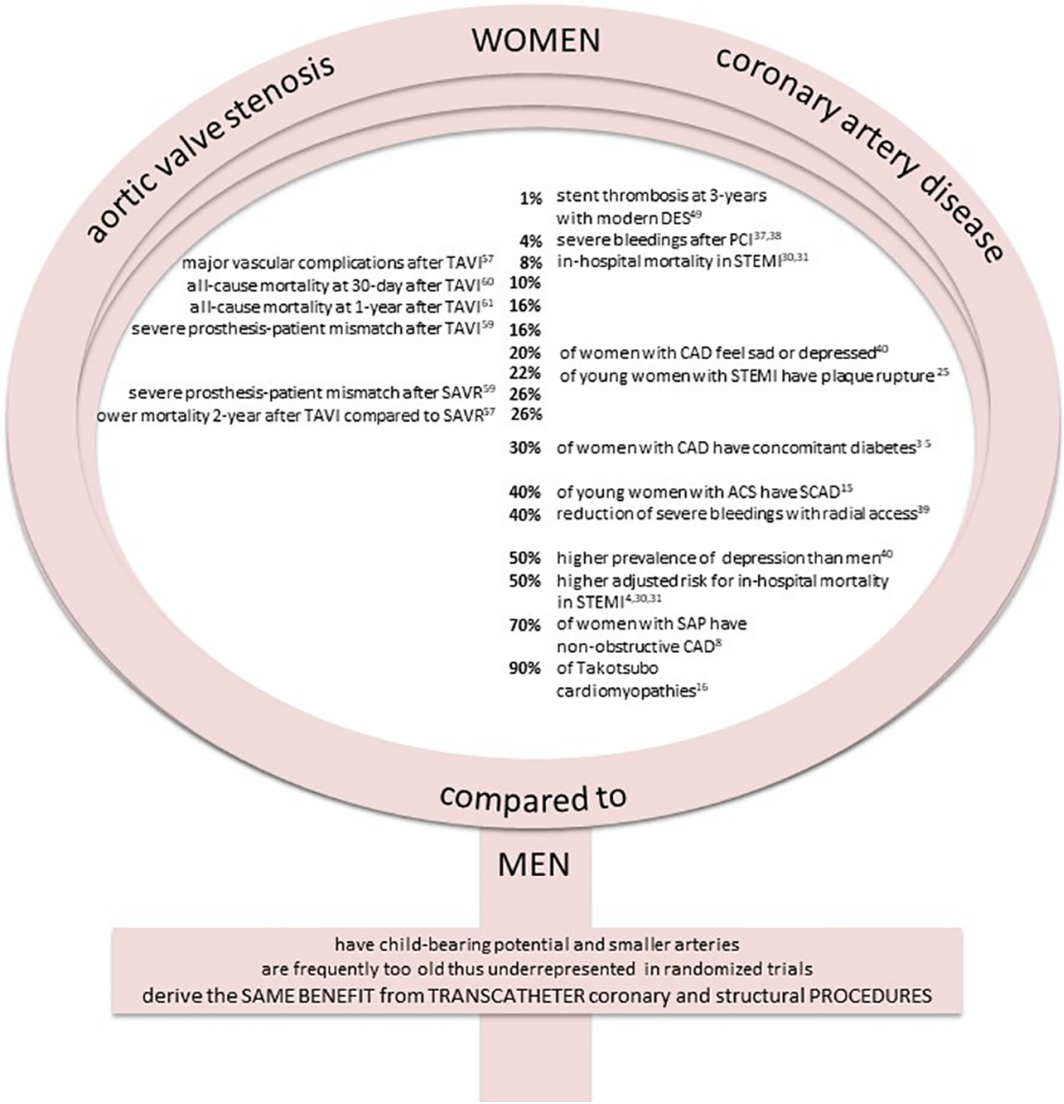
Possible differences in optimal management of ACS depending on the underlying plaque pathology
Determining sex-specific cut-off values for functional relevance of CAD on the background of pronounced microvascular dysfunction amongst women
Understanding of sex-specific outcomes to allow individualized revascularization strategies in those with complex coronary artery disease
Understanding sex-differences in outcomes following TAVI for aortic stenosis

ACS=Acute Coronary Syndrome; CAD=Coronary Artery Disease; TAVI=Transcatheter Aortic Valve Implantation.

Table 2. What Could Be Done To Improve Outcomes in Women

Larger use of adjunctive imaging tools to assist decision-making in women
Sex-specific studies in STEMI patients to assess factors potentially driving mortality differences between sexes
Sex-specific studies in complex coronary artery disease to improve outcomes in this large and growing population of women
Future research in disease mechanisms specific to each sex in those with aortic stenosis and left atrial abnormalities allowing potential individualized interventions

STEMI=ST Elevation Myocardial Infarction.



Appendix 1

Due to the higher rate of bleeding complications in women undergoing PCI, much focus has been placed on reducing bleeding events and improving outcomes. Some positive data for the use of bivalirudin, an intravenous direct thrombin inhibitor, did emerge as a possible alternative to unfractionated heparin in patients undergoing interventional procedures. A patient pooled analysis of 3 randomized controlled trials including 14,784 patients aimed to assess the effects of bivalirudin (1,870 women) versus heparin and glycoprotein IIb / IIIa inhibitor therapy (1,910 women) on bleeding rates. Despite a significantly higher rate of bleeding in women at 30 days (7.6% vs. 3.8%; $p<0.0001$), bivalirudin was shown to reduce major bleeding events in women (5.6% vs. 9.7%; $p<0.0001$) and also 12 month mortality (2.9% vs. 4.4%; $p=0.02$)[48].

In addition to the parenteral anti-thrombotic agents given during the interventional procedure, more potent anti-platelet agents have been developed which have been shown to have superior outcomes in conjunction with aspirin with less requirement for glycoprotein IIb/IIIa inhibitors. Recently, a sex specific meta-analysis of 87,840 patients (27.9% women) undergoing treatment with potent P2Y12 inhibitors (including prasugrel, ticagrelor and cangrelor) showed an increase in major bleeding in women (HR 1.28; 95% CI 0.87-1.88) as well as in men (HR 1.52; 95% CI 1.12-2.07). However, these newer drugs did reduce the risk of MACE by 14% in women (HR 0.86; 95% CI 0.78-0.94), comparable with the benefits seen in men[49] This suggests that patient sex should not be a determining factor in deciding upon the anti-platelet agent being used as both groups do have a significant benefit. Other inherent factors in women, including different pharmacokinetics, due to smaller body mass with relatively more fat and lower creatinine clearance can lead to a higher circulating level of common anti-thrombotic therapies administered during interventional procedures at a

similar dose to men. A lower body mass index, again more common in the female population, has also been shown to increase the risk of bleeding[50]. It is therefore essential that these factors are taken into account when deciding on the type and dose of pharmacological therapies given to female patients. Furthermore, the use of the radial access site is imperative to minimize the risk of bleeding in women.

Appendix 2.

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Appendix 3

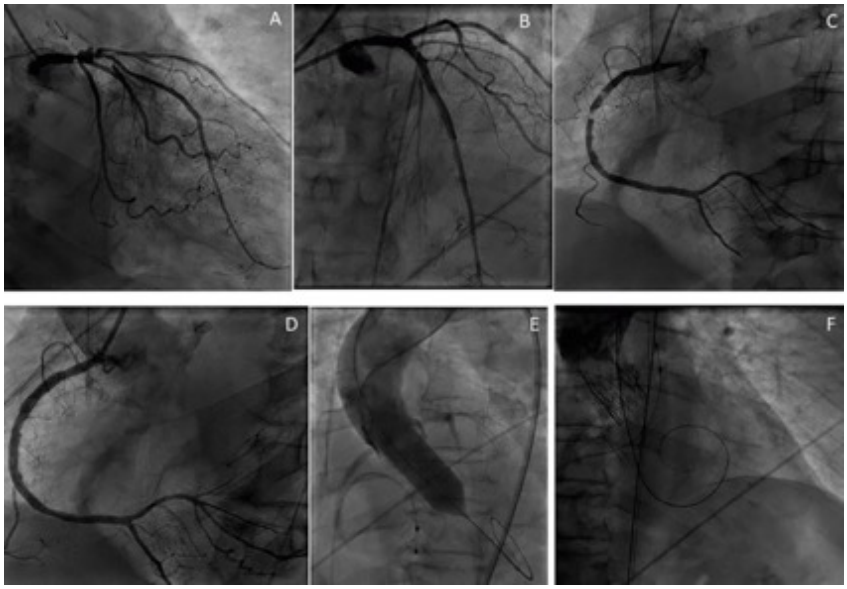
Supplementary Figure 1 shows the angiogram (panel A-B) and OCT-examinations (panel C-D) from a 51-year-old lady with anterolateral STEMI. Initial angiogram showed an occluded LAD and D1 (panel A), and wiring of the LAD revealed a spiroid spontaneous coronary dissection of both vessels. Following thrombectomy and implantation of a drug-eluting stent in D1 (TIMI 0) (panel B), there was complete resolution of ST elevations and chest pain – further intervention on the LAD (TIMI 2) was therefore not performed. By angiography after 48 hours, the LAD dissection persisted, and OCT confirmed >50 mm dissection from the ostium to the distal LAD (panel C) – longer than expected by angiography. Panel D shows serial (at 48 hours and 40 days) matched OCT cross-sections at different distances from the LAD ostium. Neither thrombus nor atherosclerosis was present at 48 hours, but a dissection exhibiting different shapes: as double lumen (A_0-B_0) with difficulty to distinguish the true (TL) from false lumen (FL); bulky flap (white arrow, C_0) at the level of a side branch (SB); and folded structure (dotted line, D_0). The trilaminar vessel structure was not visible as the intima (i) was dissected off the adventitia (a) (A_0-B_0). OCT also demonstrated deep dissections (*) behind the adventitia (A_0-C_0), and deep haematoma (**) in B_0. Angiography remained unchanged at 40 days, where OCT showed signs of healing with thickening of the dissection flap and simultaneously progressive collapse of the TL and increase of the FL (A_{40}-D_{40}). With a stable clinical course there was no need for further intervention.

Courtesy of Dr. N Amabile and Dr. M Radu from the Clinical Atlas of OCT, 2nd Edition, EUROPA Publishing 2017.

Supplementary Figure 2 shows the case of a 79 year old woman presenting to the emergency department with pulmonary edema and cardiogenic shock in the context of NSTEMI and concomitant severe aortic stenosis. At the angiogram (A and C) multi-vessel disease with

involvement of the distal left main stem was observed and treated with PCI and DES implantation from LM towards LAD, proximal LAD and RCA.(B and D) As the patient remained hypotensive despite inotropic support and IABP, balloon aortic valvuloplasty (with adequate balloon size) was performed (E). The hypotension persisted and in the presence of moderate aortic regurgitation, TAVI with Symetis M was performed (F). There was rapid hemodynamic improvement after TAVI and inotropes were discontinued day one post-operatively and the patient was discharged on the following day.

Supplementary Figure 1



Supplementary Figure 2