Results of Percutaneous Interventions with Drug Coated Balloons in Diabetic Patients with de novo Coronary Artery Lesions in University Hospital Center Zagreb

Jelovečki Đokić, Zoya

Master's thesis / Diplomski rad

2023

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:470358

University of Zagreb

School of Medicine

Zoya Jelovecki-Dokic

Results of Percutaneous Interventions with Drug Coated Balloons in Diabetic Patients with de novo Coronary Artery Lesions in University Hospital Center Zagreb

Graduate Thesis

Zagreb, 2023.

List of Abbreviations

ACS - acute coronary syndrome

BASKET-SMALL 2 - Basel Kosten Effektivitäts Trial-Drug-Coated Balloons Versus Drug-Eluting Stents in Small Vessel Interventions

BELLO - Balloon Elution and Late Loss Optimization

BENESTENT - Belgian-Netherlands STENT Study

BMI - body mass index

BMS - bare metal stents

CABG - coronary artery bypass grafting

CAD - coronary artery disease

CARDIA - Coronary Artery Revascularization in Diabetes Trial

DAPT - dual anti-platelet therapy

DCB - drug coated balloons

DEBUT- Drug-eluting Balloon in Bifurcation Lesions: A European Registry

DES - drug- eluting stent

ESC - European Society of Cardiology

EES - everolimus-eluting stent

ISR - in-stent restenosis

ISAR-DESIRE 3 - Drug Eluting Stents for In-Stent Restenosis

MACE - major adverse cardiac events

MI- myocardial infarction

NSTEMI - non-ST segment elevation myocardial infarction

PCI - Percutaneous coronary artery intervention

PEPCAD-1 - Paclitaxel-Eluting PTCA-Balloon Catheter to treat small vessel disease

PEPCAD-2 - Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease-2

PEPCAD-BIF - Paclitaxel-Eluting PTCA-Balloon Catheter for treatment of Bifurcation lesions

PEPCAD NSTEMI - Bare Metal Stent Versus Drug Coated Balloon With Provisional Stenting in Non-ST-Elevation Myocardial Infarction

PES- paclitaxel-eluting stent

PICCOLETO - Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease

POBA - plain old balloon angioplasty

REVELATION- Revascularization with Paclitaxel-coated Balloon Angioplasty Versus Drug-eluting Stenting in Acute Myocardial Infarction

RIB-V - Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent

STEMI - ST-segment elevation myocardial infarction

STRESS - North American Stent Restenosis Study

SVD - small vessel disease

SYNTAX - TAXUS drug-eluting stent vs coronary artery bypass surgery for the treatment of narrowed arteries

TLR - target lesion revascularization

Table of Contents

ABSTRACT

Introduction: The aim of this study is to assess the efficacy of drug-coated balloons (DCB) in percutaneous coronary artery interventions (PCI) in treatment of de novo coronary artery lesions in diabetic patients.

Materials and Methods: This retrospective study enrolled 225 patients that were treated at the University Hospital Center Zagreb between November 2011 and August 2022. All data were collected from the hospital documentation systems. The patients were divided into two primary groups: diabetics and non-diabetics.

Results: Out of a total of 225 patients, 59 (26.2%) were included in the diabetic group and 166 (73.8%) in the nondiabetic group. The following sociodemographic and clinical characteristics were statistically significantly different between the two groups: arterial hypertension (diabetics 98.3% vs non-diabetics 83.7% $p<0.001$), smoking status (diabetics 19% vs non-diabetics 34.8%, $p<0.030$), body mass index -BMI (diabetics 9.7 % vs non-diabetics 27.8 %, CI 27.7-28.9, $p< 0.005$) and history of prior myocardial infarction (diabetics 45.8% vs non-diabetics 30.1%, $p<0.038$). There were no significant differences between intervention indications and angiographic findings except for a significantly higher rate of triple vessel disease among diabetics (67.8% vs 40.4%, $p<0.001$) and single vessel disease in non-diabetics

(12% vs 27%, $p<0.029$). There were no statistically significant differences in early post-procedural findings or procedural complications. The mean clinical follow-up for patients was 30.6 months. The rates of angiographic follow-up were significantly higher in the diabetic group (64.4% vs 34.9%, $p<0.001$), as were the rates of elective angiographies (59.3% vs 31.9%, $p<0.001$). Out of our primary end points, only target lesion revascularization (TLR) was statistically significant higher in the diabetic group (18.6% vs 3%, $p<0.001$). New acute coronary syndrome during follow-up (diabetics 11.9% vs non-diabetics 4.2%, $P<0.055$) and re-hospitalization rates (diabetics 14% vs non-diabetics 6.1%, $p<0.087$) were higher in the diabetic group but did not reach statistical significance. Although we don't have follow-up for all patients (23 were lost for follow-up), there was no death due to cardiac causes.

Conclusion: DCB-only in PCI of de novo coronary artery lesions is associated with higher rates of TLR in diabetic patients. This doesn't affect clinical outcomes of this patients because MACE (new acute coronary syndrome and rates of re-hospitalization) although higher did not reach statistical significance. Diabetes mellitus is a predictor of worse DCB-only PCI angiographic outcomes in the novo coronary artery lesions, however; this does not render DCBs unsafe for usage.

Keywords: diabetes mellitus, drug coated balloons, percutaneous coronary artery intervention

SAŽETAK

Uvod: Cilj ovog istraživanja je procijeniti učinkovitost perkutane koronarne intervencije (PCI) pomoću balona oboženim lijekom (drug coated balloon - DCB) u "de-novo" lezijama koronarnih arterija u bolesnika sa šećernom bolesti.

Materijali i metode: Ovo retrospektivno istraživanje uključilo je 225 bolesnika koji su liječeni u Kliničkom bolničkom centru Zagreb od studenog 2011. do kolovoza 2022. Svi podaci su prikupljeni iz bolničkih dokumentacijskih sustava. Bolesnici su podijeljeni u dvije skupine: dijabetičari i ne-dijabetičari.

Rezultati: Od ukupno 225 bolesnika, 59 (26,2%) je bilo uključeno u skupinu s dijabetesom, a 166 (73,8%) u skupinu bez dijabetesa. Sljedeće sociodemografske i kliničke karakteristike značajno su se razlikovale između ove dvije skupine bolesnika: arterijska hipertenzija (dijabetičari 98,3% vs ne-dijabetičari 83,7%, $p<0,001$), pušenje (dijabetičari 19% vs ne-dijabetičari 34,8%, $p<0,030$), index tjelesne mase - BMI (dijabetičari 29,7% vs. ne-dijabetičari 27,8%, CI 27,7-28,9, $p<0,005$) i prethodni infarkt miokarda (dijabetičari 45,8% vs ne-dijabetičari 30,1%, $p<0,038$). Nije bilo statistički značajnih razlika u indikacijama za intervenciju i u angiografskim nalazima, osim značajno većeg postotka trožilne koronarne bolesti među dijabetičarima (67,8% vs 40,4%, $p<0,001$) i jednožilne koronarne bolesti kod

ne-dijabetičara (12% vs 27%, p<0,029). Nije bilo statistički značajnih razlika u ranom post-proceduralnom angiografskom rezultatu ili proceduralnim komplikacijama. Prosječno kliničko praćenje bilo je 30,6 mjeseci. Stope angiografskog praćenja bile su značajno više u skupini bolesnika s dijabetesom (64,4% vs 34,9%, p<0,001), kao i stope elektivnih koronarografija (59,3% vs 31,9%, p<0,001). Od primarnog ishoda, samo je revaskularizacija ciljne lezije (target lesion revasularization- TLR) bila statistički značajno viša u bolesnika sa šećernom bolesti (18,6% vs 3%, p<0,001). Iako su novi akutni koronarni sindrom (dijabetičari 11,9% vs ne-dijabetičari 4,2%, p<0,055) i rehospitalizacija (dijabetičari 14% vs ne-dijabetičari 6,1%, p<0,087) bili češći u bolesnika sa šećernom bolesti, nisu postigle statističku značajnost. Nitko od bolesnika nije umro tijekom kliničkog praćenja, iako nedostaju podaci za 23 bolesnika.

Zaključak: PCI pomoću DCB-a u "de-novo" lezija koronarnih arterija povezan je s većom učestalosti TLR-a u bolesnika sa šećernom bolesti što međutim, ne utječe na njihov klinički ishod. Naime, MACE (major adverse cardiovascular events) koji se sastoji od novog akutnog koronarnog sindroma i rehospitalizacije, iako viši u bolesnika sa šećernom bolesti nije postigao statističku značajnost. Iako je šećerna bolest prediktor lošijeg angiografskog ishoda u perkutanoj koronarnoj intervencji pomoću DCB-a, njihova primjena je sigurna i efikasna u tih bolesnika.

Ključne riječi: šećerna bolest, lijekom obloženi baloni, perkutana koronarna intervencija.

1. INTRODUCTION

1.1 PERCUTANEOUS CORONARY ARTERY INTERVENTION

Percutaneous coronary artery intervention (PCI) is a minimally invasive procedure used to treat coronary artery disease (CAD). Interventional cardiologists perform this technique which involves inserting a catheter into the radial or femoral artery to gain access to a narrowed or occluded coronary artery. By using either plain balloon dilatation or stent implantation, they can treat coronary artery lesions. It is one of the most common procedures performed in hospitals worldwide. According to the 2013 American College of Cardiology Foundation/American Heart Association guidelines for the management of ST-segment elevation myocardial infarction (STEMI), PCI is a Class 1 recommendation in the first 12 hours of onset of ischemic symptoms or verified STEMI and a Class 2A recommendation for the treatment of STEMI after 12 to 24 hours if ischemic pain symptoms continue (1). Similarly, European Society of Cardiology (ESC) 2017 guidelines recommend 2nd generation drug-eluting stent (DES) in primary PCI as a COR (Class of Recommendation) 1A recommendation and treatment of STEMI(2).

1.1.1 PCI in diabetic patients

Coronary artery disease (CAD) in patients with type 2 diabetes is a challenge to treat and it is a well-established independent predictor of poorer clinical outcome following treatment with

PCI (3). Diabetes results in pathophysiological derangements that contribute to worse treatment results (4). Hyperglycemia, dyslipidemia, increased end glycosylation products and insulin resistance all contribute to the accelerated development of atherosclerosis and vascular disease in the diabetic population (5). These changes induce endothelial dysfunction, platelet and coagulation abnormalities and a pro-inflammatory state leading to further challenges in CAD treatment (6). CAD in diabetic patients tends to be more complex, with widespread multi-vessel involvement due to diffuse atherosclerotic disease (4). Further treatment difficulties are also linked to the greater number of significant stenoses, long lesions, higher plaque burden, higher prevalence of small vessel disease and poorer formation of collateral vasculature (7,8). CAD in diabetic patients also tends to present more often with silent ischemia and atypical symptoms, potentially due to autonomic neuropathy, leading to late diagnosis and more progressive disease upon discovery (9,10). The later stage of disease discovery further contributes to worse results.

Higher rates of in-stent restenosis (ISR), target lesion revascularization (TLR) and lower rates of survival have all been associated with PCI in diabetic patients (11). The SYNTAX trial enrolled 1800 patients to either treat three-vessel or left main disease with coronary artery bypass grafting (CABG) or PCI with use of a 1st generation stent. At 10year follow-up, PCI was associated with higher rates of all-cause death compared with CABG (34% vs 29%, HR 1·18, 95% CI 1·00–1·39) and CABG demonstrated a survival benefit in three-vessel disease (12). However, it is important to note that since the SYNTAX trial, we have switched to using 2nd generation DES which are associated with better 3-year outcome (13). Despite, improvements in DES's technology other trials have still found CABG to be the superior revascularization technique in diabetic patients with complex multivessel disease. The CARDIA trial demonstrated non-inferiority of DES compared with CABG at one year follow-up, however; the PCI group

was associated with significantly higher rate of repeat revascularization (2.0% vs. 11.8%, $p < 0.001$) (14). The FREEDOM was another large-scale trial held to evaluate the use of PCI compared with CABG, enrolling 1900 patients. Similarly, the trial demonstrated higher rates of myocardial infarction and cardiovascular death at 1 year follow-up, which was greatly attributed to the higher needs to repeat revascularization in the PCI group (15).

1.1.2 History of PCI: Plain old balloon angioplasty and Bare Metal Stents

Percutaneous coronary artery intervention first came into use in the late 1970s revolutionizing treatment of CAD. Initial procedures involved the usage of plain balloon angioplasty (POBA), however; this initial form of PCI was associated with many procedural complications such as early vessel recoil, dissection and endothelial vessel dysfunction leading to thrombosis (16). In order to overcome these early complications of POBA, bare metal stents (BMS) came into usage. Major clinical trials such as the BENESTENT and STRESS trials, demonstrated that BMS had less rates of major cardiac events a year after implantation and lower rates of target lesion revascularization (TLR) (17,18). However, there were still complications associated with BMS which included fatal stent thrombosis, ISR, difficulty with stent delivery and need for repeat revascularization (16). This heralded the development of first-generation DES.

1.1.3 Drug-eluting stents

DES are composed of three components; metal scaffolding, a polymer which acts as a reservoir for the drug and the drug itself. In the first generation DES the most commonly used agents were sirolimus and paclitaxel. 1st-generation DES were also associated with

complications, multiple studies reported high rates of late complications of stent thrombosis which resulted in high rates of reinfarction and death (19). An analysis that pooled data from 14 trials and that included 4958 patients by Kastrati et al, demonstrated these complications by reporting that sirolimus eluting stents had similar outcomes in terms of long-term survival and cardiac death as compared with bare metal stents, however; a year after intervention there were higher rates of stent thrombosis associated with sirolimus stents (20). This development of late stent thrombosis is attributed to incomplete re-reendothelialization due to drug-induced inhibition of endothelial cell proliferation, accelerated neoatherosclerosis, stent malpositioning and polymer-induced vessel wall inflammation (21).

In order to combat the continued issue of late stent thrombosis, 2nd generation DES were created. The drugs used in these stents, everolimus and zotarlimus, which are more lipophilic and are less toxic anti-proliferative drugs (22). Likewise, the metal scaffolding of the stent was also upgraded and improved in order to make them easier to deliver and deploy (16). Palmerini et al. collected data in a meta-analysis from 51 trials with a total of 52,158 patients comparing different stents, and their results showed that 2nd generation DES had significantly lower rates of late stent thrombosis when compared with the 1st generation (23). However, it is important to mention that the benefits of BMS, 1st DES and 2nd DES outweigh the risks and are the mainstay of CAD treatment in today's world.

1.2 DRUG COATED BALLOONS

Drug coated balloon (DCB) consist of a balloon coated with an antiproliferative agent that when expanded for 30-60 seconds transiently releases the agent to the vessel wall without leaving behind an implant (24). Their benefits over stents include the lack of a metallic scaffold which decreases the risk of both early and late thrombosis and also present a potential for shorter

duration of dual anti-thrombotic therapy after PCI (25). However, there have been some complications associated with DCB, such as vasospasm, early recoil and vessel dissection (26). DCB remain a novel treatment option within the field of interventional cardiology and their usage in clinical medicine is still being established.

1.2.1 Technology of DCBs

DCBs are comprised of a balloon, antiproliferative agent and excipient. Paclitaxel is the most commonly used agent today, though several studies have tested the usage of sirolimus (24). Paclitaxel still remains the agent of choice because it has better tissue absorption and retention (27). Beyond just the drug, the balloon is also coated in an excipient which helps facilitate delivery to the vessel wall. The excipient varies based on the manufacturer of the DCB, the most commonly used excipients are urea, polysorbate/sorbitol, polyethylene glycol (27). Prior to DCB deployment the lesion should be prepared with predilatation in order to achieve optimal angiographic results (28).

1.3 CLINICAL APPLICATIONS OF DCBS

The 2020 International Consensus Report on DCB discusses the usage and recommendations regarding DCBs. The conditions that DCBs have been studied in the most and are currently most recommended in are ISR, small vessel disease, and bifurcation lesions (28). DCBs could also provide advantageous treatment for patients who are at high risk of bleeding. According to the International DCB Consensus group, a 4-week duration of dual-antiplatelet therapy (DAPT) following DCB-only angioplasty is satisfactory and a 6–12-month duration if used in combination with a bare metal stent (28). The potential for a shortened course of dual-antiplatelet therapy after the use DCB has great clinical applications and could help overcome the challenge of treating patients who have contraindications to long term DAPT.

Furthermore, there are limited data on the usage of DCBs in large vessel disease, acute coronary syndromes (ACS) and diabetic patients and further studies are required for all of these conditions.

1.3.1 DCBs in ISR

In-stent restenosis is a narrowing of a previously stented coronary artery lesion. It presents a common complication after coronary stenting and can be challenging to treat. DCB usage for treatment of ISR has been well studied. The PEPCAD-2 was the first trial that compared DCB and POBA in DES restenosis. They found that late lumen loss was significantly lower with DCB demonstrating their superiority (29). The RIBS-V trial went on to compare the results of BMS ISR treatment with either DCB or everolimus-eluting stents (EES). While late angiographic results were superior in the EES arm, the long-term results of DCBs were also excellent and they concluded DCBs to be non-inferior to EES (30). Another trial to confirm the safety of using DCB in DES ISR, was the ISAR-DESIRE 3 trial which compared DCB usage to both POBA and PES (paclitaxel-eluting stent). The ISAR-DESIRE 3 trial enrolled a total of 402 patients and recently published the findings after 10-year follow-up. The trial showed that the primary outcome composed of cardiac death, target vessel myocardial infarction, TLR and target lesion thrombosis was significant higher in POBA versus DCB and paclitaxel-eluting stent (PES)(31). However, primary outcomes between DCB and PES were similar and there were no statistical significances, indicating that DCB is non-inferior to PES for treatment of DES-ISR (31). Other studies further established the non-inferiority of DCBs in ISR treatment and DCBs are currently a Class 1A recommendation for BMS and DES ISR treatment according to the ESC guidelines (32).

1.3.2 DCBs in Bifurcation Disease

Bifurcation lesions have been a challenge for interventional cardiologists to treat, with higher rates of procedural complications, higher rates of ISR and inferior long term post-procedural outcomes (33). Bifurcation lesions refer to a vessel narrowing occurring at the junction of two vessels. The goal of intervention is restoring perfusion to both, the main vessel and side branch. The PEPCAD-BIF was the first randomized trial to compare the usage of DCB to POBA in treatment of distal main branch or side branch disease. The study enrolled 64 patients and concluded that DCB are superior in treatment to POBA for distal main or side branch, due to lower rates of late lumen loss (34). The DEBUIT trial demonstrated that DCB in the side branch after BMS implantation in the main branch was non-superior to POBA and that DES was superior to both DCB and BMS treatments (35). Burch et al. published an observational prospective study that followed 127 patients and at 9-month follow-up found rates of 4.6% TLR and 6.2% major adverse cardiac events (MACE) in patients whose bifurcation lesions were treated with "DCB-only" (36). The results of the study suggest that the DCB-only approach could be beneficial in selected bifurcation lesions.

Overall, the role of DCBs in treatment of bifurcation lesions needs to be studied further. While studies show that in some bifurcation lesions DCB can be used to treat the side or main branch further randomized trials are needed comparing DCBs with DES (37). The International Consensus Report on DCBs states that DCBs can be used for main or side branch lesions, while the ESC recommends DES usage in the main branch and suggests that DCB treatment of side branches might be preferable to POBA (28).

1.3.3 DCBs in de novo small vessel disease

DCBs have also been studied for the treatment of de novo small vessel coronary artery disease. The definition of small vessel disease (SVD) has been broadly defined as coronary vessels measuring less than 2.75-2.80 mm in diameter (criteria vary in literature) (38). While DES are effective at treating small vessel disease their usage results in a higher percentage of late lumen loss respective to the smaller vessel caliber, this leads to higher rates of ISR and clinical events (39). Several clinical studies have been conducted to determine whether DCBs could be an effective treatment for de novo small vessel coronary artery disease. One of the first larger trials, was the PICCOLETO trial which compared the use of the Dior DCB (coated with paclitaxel) compared to the Taxus (paclitaxel) DES. They planned to enroll 80 patients but stopped at 60 due to superior outcomes in the Taxus cohort (40). The study was stopped due to a strong trend of better clinical outcome in the Taxus group (13.8% vs 35.7%, $p<0.054$), which was likely due to the higher rates of TLR in the Dior DCB group (32.1% vs 10.3% $p<0.15$)(40). Lack of lesion predilatation with POBA, high rate of bail-out stenting without taking geographical mismatch into consideration and the later demonstration that the Dior balloons elute lower concentrations of paclitaxel are all factors that contributed to the poor outcomes of the PICCOLETO trial (41). Studies performed more recently and after the PICCOLETO trial have demonstrated much better results.

The PEPCAD-1 SVD trial was one of the first to test the use of DCBs in SVD, comparing them with POBA usage. It demonstrated that after 9 months DCB treatment has superior results with significantly less late lumen loss (LLL) (42). One of the largest trials to date on the use of DCBs in de novo SVD is the BASKET-SMALL 2 trial. The BASKET-SMALL 2 trial enrolled 883 patients that were either treated with DCB or DES, the end results showed

similar rates of major adverse cardiovascular events - MACE (7.3% vs 7.5%, p<0.9180) and TLR (3.4 v 4.5%, p<0.4375) between the two groups at 12-month follow-up and the study demonstrated non-inferiority of DCB treatment (43). Furthermore, a three-year follow-up study was published from the BASKET-SMALL 2 trail. The data further support the non-inferiority of DCB in SVD treatment with findings of low rates of clinical events in DCB-only treatment, lower rates of bleeding and stent thrombosis and similar all cause morality between the two groups (44). The results of the smaller BELLO trial showed decrease in late lumen loss and similar outcomes of death, TLR and myocardial infarction (45).

1.3.4 DCB in ACS

DCBs usage in treatment of ACS is still not well established. The BASKET-SMALL 2 trial enrolled patients with any indication for PCI and performed a subgroup analysis on the use of DCB versus DES in ACS. It demonstrated non-inferiority of DCB to DES treatment in ACS at 3-year follow-up (46). The PEPCAD NSTEMI trial compared the usage of DCBS to BMS or DES in the setting of non-ST segment elevation myocardial infarction (NSTEMI). The trial enrolled at total of 210 patients diagnosed with NSTEMI. The study found that at 9-month follow-up there was no statistical significance between any of the relevant clinical endpoints which included TLR, MACE, rates of death, myocardial infarction and PCI of other vessels (47). The REVELATION study investigated treatment of STEMI with DCB or DES and found comparable results to the PEPCAD-NSTEMI trial at two-year follow-up (48).

1.3.5 DCBs in diabetics

DCBs could be a viable treatment in diabetic patients, especially considering diabetics tend to have long, complex lesions in small caliber vessels with low coronary vasodilator reserve (49). However, their usage has not been well studied in this population. Subgroup analysis of the

BASKET-SMALL 2 trial sought to compare the outcomes of DCBs and DES in diabetic patients. It was found that rates of MACE, nonfatal MI and death were higher in the diabetic population and similar in both DES and DCB group, however; TLR was significantly lower with DCBs (50). The BELLO study demonstrated similar rates in late lumen loss even in the diabetic subgroup when compared with DES treatment (45). Even though these findings demonstrate that the usage of DCB to DES could be advantageous in some settings, there is little data on how diabetes effects the results of "DCB-only" angioplasty and whether similarly to treatment with DES it is associated with higher rates of TLR.

2. HYPOTHESIS

The hypothesis of our study is that "DCB-only" PCI in treatment of de novo coronary artery lesions will produce similar outcomes in terms of TLR and MACE (new acute coronary syndrome, rates of rehospitalization and death of cardiac causes) among diabetic and non-diabetic patients.

3. STUDY GOALS

Our primary end goals were to establish the rates of TLR and MACE consisting of new acute coronary syndrome, rates of rehospitalization and death of cardiac causes, among diabetic and non-diabetic patients that underwent "DCB-only" angioplasty for the treatment of de novo coronary artery lesions.

Specific goals:

1. Compare sociodemographic and clinical characteristics among diabetics and non-diabetics.
2. Compare indications for intervention and pre-procedural angiographic findings among diabetics and non-diabetics.

3. Compare procedural complications among diabetics and non-diabetics.
4. Compare early post-procedural angiographic outcomes among diabetics and non-diabetics.
5. Compare clinical and angiographic follow-up among diabetics and non-diabetics.

4. MATERIALS AND METHODS

4.1 Patients selection criteria

Two hundred and twenty-five patients were included in our retrospective study on the use of DCBs in de novo coronary artery lesions. All patients were treated at the University Hospital Centre Zagreb, Clinic of Cardiology between November 2011 and August 2022. Data were collected retrospectively from the hospital's medical documentation systems and the catheterization lab software; BIS and cardioreport. The patients were divided into two groups; diabetics and non-diabetics. Diabetics were defined as patients who had an established diagnosis of diabetes mellitus type 2 prior to the performance of "DCB-only" PCI. Primary outcomes of the study were the rate of re-hospitalization due to ACS or other cardiac events and rate of TLR. We excluded cases in which DCB were used to treat ISR and cases where hybrid treatment was used on the same vessel or bifurcation (DCB+DES).

4.2 Data Collection

The following sociodemographic data were collected: age, sex, BMI, smoking status, hypertension, chronic kidney disease and hyperlipidemia. Cardiac amnestic data was likewise

collected and included the following: past myocardial infarction, past percutaneous coronary artery intervention and history of coronary artery bypass grafting (CABG).

Data on the indication for coronary artery intervention were collected. This was divided broadly into acute coronary syndrome (ACS) and chronic coronary artery disease. ACS was further subdivided into NSTEMI, STEMI and unstable angina. Angiographic findings prior to intervention included: single, double or triple vessel CAD, vessel of lesion location, percentage of vessel stenosis and presence of bifurcation disease. Intervention data were collected as follows: number of DCBs deployed during the procedure, average diameter and length of DCBs and the amount of residual vessel stenosis after DCB deployment. Procedure complications were divided into three categories: dissection, thrombosis and stent implantation (stent bail out).

Follow-up was divided into two major categories: clinical and angiographic follow-up. Clinical follow-up included any follow-up at an outpatient clinic or re-hospitalization at the University Hospital Centre Zagreb. Clinical follow up did not have to be at the cardiology clinic, any patient visit to the University Hospital Centre was taken as follow up. Loss to follow-up were patients who had not returned to our hospital since and were not able to be contacted via phone. The date of the patient's most recent clinical follow up was included. Clinical follow up was calculated as months from the date of procedure to the patient's last hospital visit. Angiographic follow-up was defined as elective coronary angiography or coronary angiography performed due to the patient presenting to the hospital with ACS necessitating invasive imaging.

Our included primary end points were major adverse cardiac events defined as rehospitalization, new acute coronary syndrome, mortality and TLR. TLR was further subdivided into TLR discovered during elective angiographic follow-up or TLR presenting as new ACS.

4.3 Statistical Analysis

Data were reported by calculating the mean of continuous variables and absolute frequencies of categorical data. Means were compared by using the t-test and proportions were compared with the chi-squared test. Comparison was performed between the diabetic and non-diabetic group for each category of variables; sociodemographic data, indication for intervention, angiographic findings, results of the intervention, complications, follow up and primary end points. *P* value of <0.05 was considered to be statistically significant.

5. RESULTS

5.1 Sociodemographic Data

Out of the 225 patients included in the study, 26.2% (n=59) had diabetes at the time they underwent PCI. Sociodemographic data are reported in **Table 1.** The mean age of diabetic patients was 70.0 years, while for non-diabetic patients it was 67.3 years. Overall age of included patients ranged from 44-97 years. The rate of females and males in each group was also similar, with 71.2% of patients with diabetes being male as compared with 72.3% of non-diabetics. There were statistical differences between the two groups in the rates of arterial hypertension, smoking, body mass index (BMI), and incidence of previous myocardial infarction. Arterial hypertension was diagnosed in 58 diabetics and 139 non-diabetics (98.3% vs 83.7% p<0.001). The overall average BMI was 28.3 kg/m2, in the diabetic group it was significantly higher with the average being 29.7 kg/m2 (CI 95%, 28.5-30.9). BMI ranged from 17-43.7 kg/m2 over both groups. A

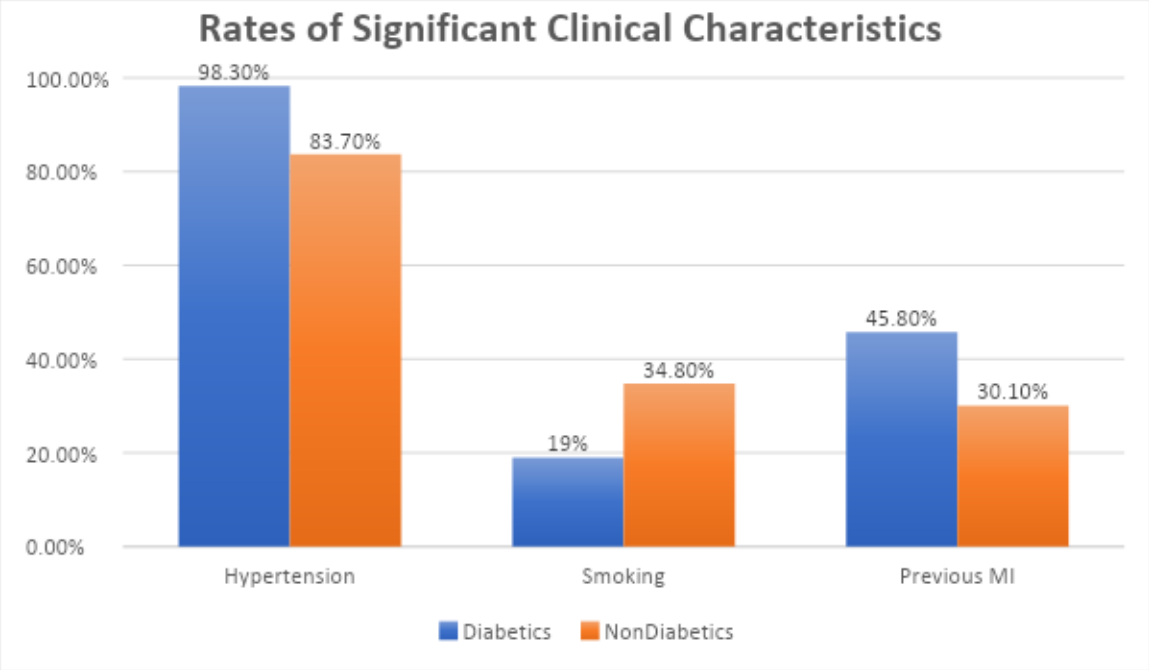
weaker statistical significance in the prevalence of smokers was present; 11 diabetics and 56 non-diabetics (19% vs 34.8%, p<0.030). A weak statistical significance was also found in the number of patients who had a previous myocardial infarction, 27 diabetics and 50 non-diabetics (45.8% vs 30.1%, p<0.038). The rest of the sociodemographic variables were not significant between the two groups. **Figure 1** presents significant clinical data.

Table 1 Sociodemographic data and history

	Overall (n=225)		range	Diabetes (n=59)		Non-diabetes (n=166)		P
age	68.1	66.5; 69.7	44-97	70.0	67.3; 72.6	67.3	65.6; 69	0.101
Sex (male)	162	72%	-	42	71.2%	120	72.3%	0.867
hypertension	197	87.6%	-	58	98.3%	139	83.7%	0.002*
smoking	67	29.8%	-	11	19%	56	34.8%	0.030*
BMI (kg/m^2)	28.3	27.7; 28.9	17-43.7	29.7	28.5; 30.9	27.8	27.1; 28.4	0.005*
CKD	15	6.7%	-	5	8.5%	10	6%	0.547
hyperlipidemia	175	77.8%	-	46	78%	129	77.7%	0.563
previous MI	77	34.2%	-	27	45.8%	50	30.1%	0.038*
previous PCI	88	39.1%	-	27	45.8%	61	36.7%	0.277
previous CABG	2	0.9%	-	1	1.7%	1	0.6%	0.457

numbers are mean (95% CI), or absolute (relative) frequency; means were compared using the t-test; proportions were compared using the χ^2- test; BMI – body mass index; CKD – chronic kidney disease; MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; *statistically significant

Figure 1 Rates of Hypertension, smoking and previous myocardial infarction (MI)



5.2 Indications for intervention and prior angiographic findings

There was no statistical significance between any of the indications for PCI between diabetics and non-diabetics**.** One hundred twenty patients underwent PCI due to ACS, the rates between groups were not significant for NSTEMI (diabetics 20.3 vs non-diabetics 32.5%, $p<0.096$), STEMI (diabetics 13.6% vs non-diabetics 15.1%, $p>0.999$) and unstable angina (diabetics 11.9% vs non-diabetics 9%, $p<0.610$). One hundred and four patients were scheduled for an elective PCI due to the presence of chronic coronary artery disease and there was no statistical significance between the two groups (diabetics 54.2% vs non-diabetics 43.3%, $p<0.225$).

Most patients in the study had triple-vessel disease at the time of the percutaneous intervention, with a significant difference between the two cohorts. Forty diabetic patients

compared with 67 non-diabetic patients presented with triple vessel disease (diabetics 67.8% vs nondiabetics 40.4%, p<0.001). On the other hand, there was significantly more non-diabetic patients who presented with single vessel disease (diabetics 12% vs nondiabetics 27%, p<0.029). **Figure 2** displays the rates of single versus triple vessel disease. The most commonly involved vessel in both groups was the first obtuse marginal branch of the left circumflex artery, with 26 lesions in the diabetic group and 13 in the non-diabetic group. The most common indication for intervention was a 90-99% subocclusive stenosis with no statistically significant difference between the groups (diabetics 45.8% vs non-diabetics 59.6%, p<0.216). The results are displayed in **Table 2** and **Table 3**.

Table 2 Indications for intervention

	Overall (n=225)		Diabetes (n=59)		Non-diabetes (n=166)		P
NSTEMI	66	29.3%	12	20.3%	54	32.5%	0.096
STEMI	33	14.7%	8	13.6%	25	15.1%	>0.999
Unstable angina	22	9.8%	7	11.9%	15	9%	0.610
Chronic CAD	104	46.7%	32	54.2%	72	43.3%	0.224

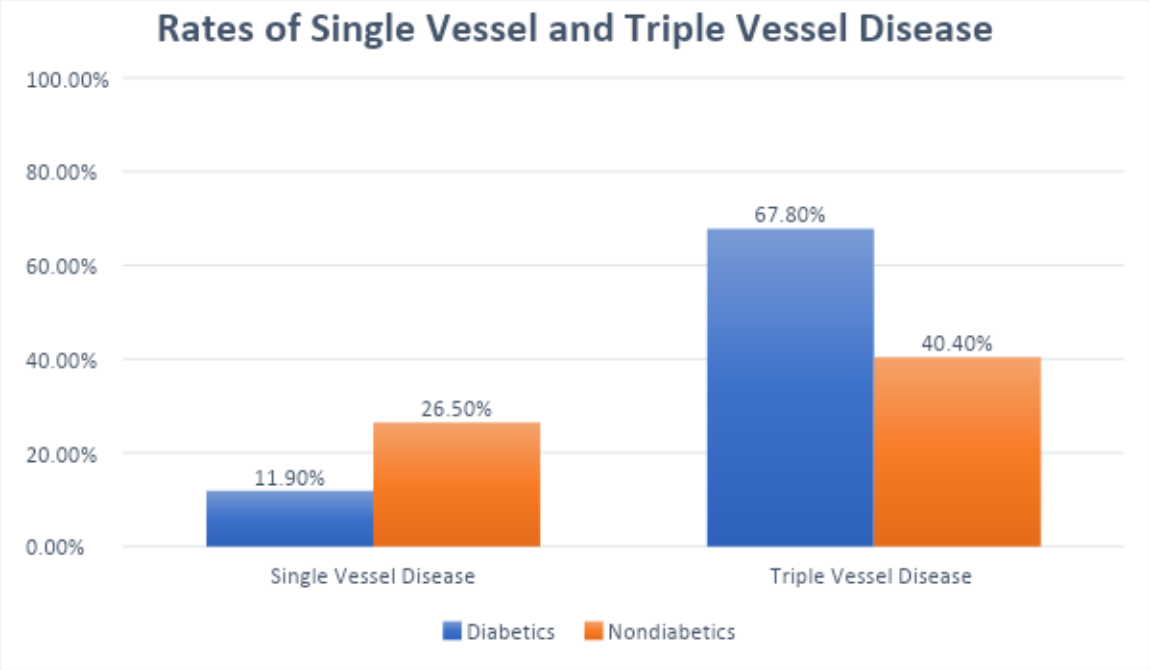
numbers are absolute (relative) frequency; proportions were compared using the χ^2- test; NSTEMI – Non-ST-segment elevation myocardial infarction; STEMI – ST-segment elevation myocardial infarction; CAD – coronary artery disease

Table 3 Angiographic findings

	Overall (*n*=225)		Diabetes (*n*=59)		Non-diabetes (*n*=166)		*P*
Single vessel disease	51	22.7%	7	11.9%	44	26.5%	0.029*
Two vessel disease	68	30.2%	12	20.3%	56	33.7%	0.069
Three vessel disease	107	47.6%	40	67.8%	67	40.4%	<0.001*
Involved vessel							
RIM			7		6		
pLAD			8		1		
mLAD			14		7		
dLAD			4		2		
D1			21		6		
D2			6		1		
pLCx			6		4		
mLCx			12		6		
dLCx			6		2		N/A
OM1			26		13		
OM2			14		1		
OM3			3		0		
OM4			1		0		
pRCA			2		0		
mRCA			5		2		
dRCA			7		0		
PD			18		5		
RPL			5		3		
RIM			7		6		
% stenosis[α]			9/22/27	15.5/37.9/45.8	23/44/99	13.9/26.5/59.6%	0.216
50-70%			9	15.5%	23	13.9%	
70-90%			22	37.9%	44	26.5%	
90-99%			27	45.8%	99	59.6%	

numbers are absolute (relative) frequency; proportions were compared using the χ^2- test; *-statistically significant

Figure 2 Single versus Triple Vessel Disease



5.3 Results of "DCB-only" PCI

There were no statistical differences in the presence of bifurcation lesions with an overall frequency of 23% in diabetics and 29% in non-diabetics. The characteristics of the DCBs were also not significant between the two groups. The mean diameter of DCB that was used was 2.47 millimeters (mm) with a confidence interval of 2.41-2.53 mm. The mean diameter of DCB used, was slightly larger in the diabetic group (diabetics 2.48 vs nondiabetics 2.46, CI 2.41-2.53, $p<0.075$). The mean length of DCB used was 20.6 mm between both groups. The DCBs used averaged shorter in the diabetic group (diabetics 20 vs nondiabetics 21, CI 95% 19.8-21.3, $p<0.308$). Likewise, there was no significant difference in the residual stenosis after DCB deployment. For both groups most patients had a residual stenosis of less than 20% (diabetics 52.6% vs non-diabetics 56.6%, $p<0.385$). The results are presented in **Table 4.**

Table 4: Intervention Findings and Results

	Overall (n=225)		Diabetes (n=59)		Nondiabetics (n=166)		*P*
bifurcation lesion			14	23.7%	48	28.9%	0.500
Number of DCB (1/2/3)			46/13/0	78/22/0	146/18/2	88/10.8/1.2	0.075
Average DCB diameter	2.47	2.41;2.53 (2-4)	2.48	2.38; 2.58	2.46	2.40; 2.52	0.713
Average DCB length	20.6	19.8;21.3 (10-40)	20	19; 21	21	20; 22	0.308
Residual stenosis[β]			30/19/2/5/1	52.6/33.3/3.5/8.8/1.8	94/50/11/11/0	56.6/30.1/6.6/6.6/0.0	0.385
<20%			30	52.6%	94	56.6%	
20-30%			19	33.3%	50	30.1%	
31-40%			2	3.5%	11	6.6%	
41-50%			5	8.8%	11	6.6%	
>50%			1	1.8%			

numbers are mean (95% CI), or absolute (relative) frequency; numbers are absolute (relative) frequency; proportions were compared using the χ^2- test; DCB- drug coated balloon; diameter and length are measured in millimeters

5.4 Procedure Complications

Overall, 13 (5.8%) patients received a stent during PCI. Eleven (4.9%) patients had vessel dissection which necessitated stent implantation, termed "stent bail out" and 3 patients received a stent due to vessel recoil after DCB and an angiographic unacceptable result. There were no cases of acute vessel thrombosis. There was no statistical significance in procedure complications between the two groups. Seven percent of diabetics suffered from intraprocedural

vessel dissection as compared with 4% of non-diabetics. No complications resulted in intraprocedural patient mortality. The results are displayed in **Table 5.**

Table 5 Complications

	Overall (*n*=225)		range	Diabetes (*n*=59)		Non-diabetics (*n*=166)		*P*
Dissection	11	4.9%	-	4	6.8%	7	4.2%	0.485
Thrombosis	0	-	-	-	-	-	-	-
Stent implantation	13	5.8%	-	5	8.5%	8	4.8%	0.333

numbers are mean (95% CI), or absolute (relative) frequency; means were compared using the t-test; proportions were compared using the χ^2- test

5.5 Angiographic and Clinical Follow-up

The mean clinical follow-up for patients included in the study was 30.6 months with a confidence interval of 26.8-34.5 months. The range of months of clinical follow up was from 0-132 months. There were 23 patients who were lost to follow-up, accounting for the value of 0 months clinical follow-up. There was no significant difference in the clinical follow-up between the two groups. Overall, 96 patients (38 diabetic patients and 58 non-diabetics) included in the study were followed up with coronary angiography. There was a statistically significant difference between the two groups (diabetics 64.4% vs non-diabetics 34.9%, $p<0.001$). Angiographic follow-up was subdivided into elective angiographic follow-up or occurrence of new ACS. Six patients received both elective angiographies and also returned to the hospital with new ACS therefore receiving coronary angiography twice in the follow-up period. Four of these patients were from the diabetic group. Overall, 14 patients were re-admitted to the hospital due to new ACS (7 diabetics and 7 non-diabetics), there was no statistical difference (diabetics

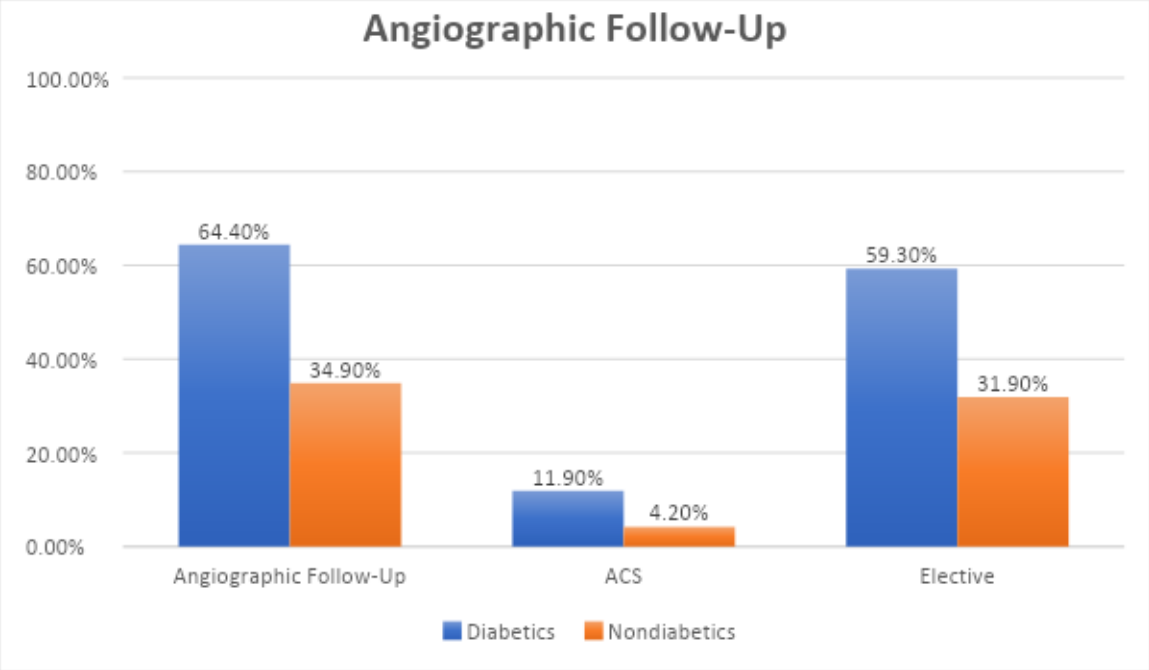
11.9% vs non-diabetics 4.2%, P<0.055). Overall, 88 patients (35 diabetics and 53 non-diabetics) were scheduled for elective angiographic follow-up, the rate of scheduled diabetics was statistically higher (diabetics 59.3% vs nondiabetics 31.9%, p<0.001). The results can be found in **Table 6** and **Figure 3.**

Table 6 Clinical follow up and Angiographic FU in ACS or elective

	Overall (n=225)		Range	Diabetes (n=59)		Non-diabetics (n=166)		*P*
Angiographic FU	96	42.7%	-	38	64.4%	58	34.9%	<0.001*
Acute coronary syn	14	6.2%	-	7	11.9%	7	4.2%	0.055
Elective	88	39.1%	-	35	59.3%	53	31.9%	<0.001*
Clinical FU	30.6	26.8;34.5	0-132	30	24; 36	31	26; 35	0.808

numbers are mean (95% CI), or absolute (relative) frequency; means were compared using the t-test; proportions were compared using the χ^2- test; FU- follow-up; clinical follow-up is measured in months; *statistically significant

Figure 3 Angiographic Follow-up



5.6 Primary End-Points

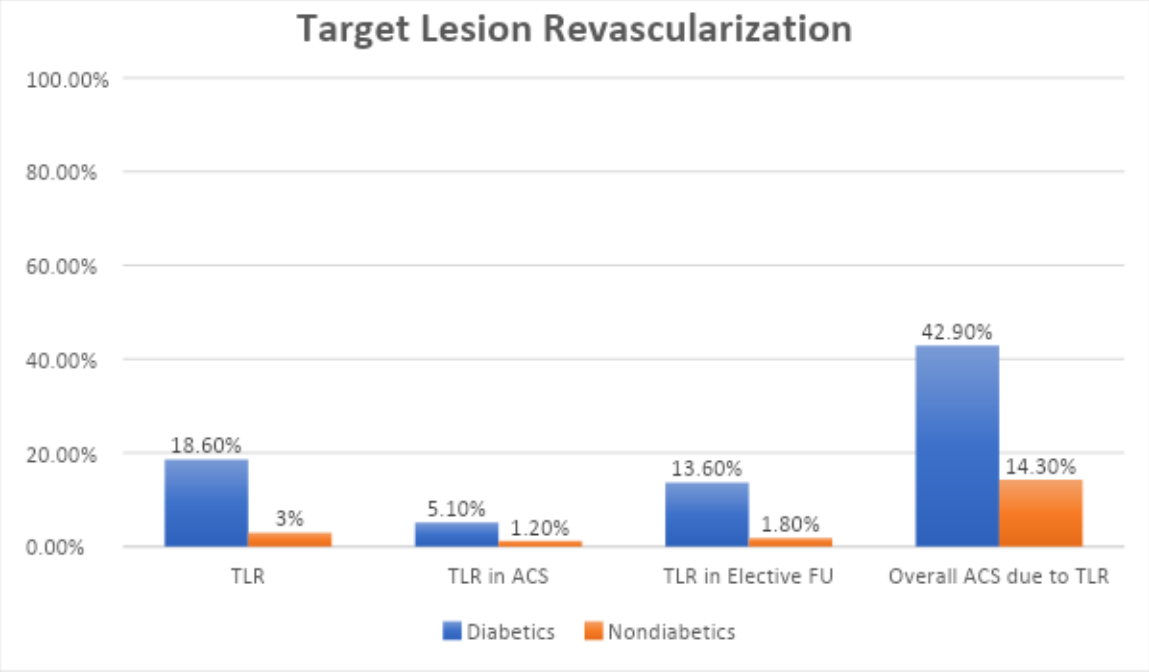
One of our primary end points was the re-hospitalization rate due to cardiac events which occurred in 18 (9%) patients. Fourteen of these patients were hospitalized due to ACS and 4 due to other cardiac events. Eight diabetic patients were re-hospitalized and 10 non-diabetic patients, there was no statistical difference between the two groups (diabetics 14% vs non-diabetics 6.1%, $p<0.087$). Target lesion revascularization, our other primary end goal, occurred in 16 (7.1%) patients overall, 11 in the diabetic group and 5 in the non-diabetic group. The rate of TLR between the two groups was statistically significant (diabetics 18.6% vs non-diabetics 3%, $p<0.001$). Eleven patient (8 diabetics and 3 non-diabetics) received TLR during an elective coronary angiography (diabetics 13.6% vs non-diabetics 1.8%). Four cases of TLR presented as new ACS with 3 patients in the diabetic group and 1 patient in the non-diabetic group (5.1% vs 3.0%). The results are displayed in **Table 7** and **Figure 4.**

Table 7 Primary endpoints

	Overall (n=225)		range	Diabetes (n=59)		Non-diabetes (n=166)		*P*
Rehospitalization	18	9.0%	-	8	14%	10	6.1%	0.087
TLR	16	7.1%	-	11	18.6%	5	3%	<0.001*
TLR in ACS	5	2.2%	-	3	5.1%	2	1.2%	
TLR in elective FU	11	5.9%	-	8	13.6%	3	1.8%	

numbers are mean (95% CI), or absolute (relative) frequency; means were compared using the t-test; proportions were compared using the χ^2- test; FU – Follow-up; TLR – Target lesion revascularization; *statistically significant

Figure 4. Target Lesion Revascularization



6. DISCUSSION

Our retrospective study aimed to determine whether DCBs were associated with worse post-procedural outcomes when used for the treatment of de novo coronary artery lesions in diabetics. While there have been clinical trials to assess the use of DCBs in treating de novo coronary artery lesions, their use in the diabetic population has not been well established. Our primary end goals were the rates of TLR and MACE defined as re-hospitalization, new acute coronary syndrome or mortality of cardiac cause. TLR was significantly higher in the diabetic group (19% vs 3% $p<0.001$). Re-hospitalization (14% vs 6% $p<0.087$) and ACS (11.9% vs 4.2%, $p<0.055$) were also higher in the diabetic group, however; there was no statistical significance reached in either. There were no cases of mortality in either group.

6.1 Sociodemographic and clinical factors

Certain sociodemographic factors potentially contributed to the worse outcomes in our diabetic group. Diabetic patients included in our study were found to have significantly higher rates of arterial hypertension (98% vs 84% $p<0.002$). Arterial hypertension, even in the absence of diabetes, is an important risk factor for the development of coronary artery disease (51). The combination of diabetes and concurrent arterial hypertension was shown to be associated with an increase in major adverse cardiac events following PCI, and both are clinical predictors for target lesion revascularization (52,53). Another risk factor for CAD, body mass index (BMI), was also found to be significantly higher in the diabetic group. This finding is in accordance with current data, that indicates that one of the greatest risk factors for the development of type 2 diabetes is high BMI (54). The mean BMI in diabetics was 29.7 (CI 95%, 28.5-30.9, $p<0.005$). A BMI of

30.0 and above is considered obese, so the mean of our diabetic group was right at the border, with the upper boundary of our standard deviation crossing into obesity. Beyond BMI being one of the greatest risk factors for developing diabetes, higher BMI in diabetics further correlates with an increase of cardiovascular complications in this population (55).

Patients in our diabetic group had higher rates of previous myocardial infarction (46% vs 30% $p<0.038$). Diabetic patients have a higher prevalence of CAD than the general population and are more likely to suffer from a myocardial infarction which is a common cause of morbidity among this population (6). Therefore, the finding of more diabetics having a history positive for myocardial infarction is in accordance with current data. Further, ACS tends to be the initial presentation of CAD in diabetics.

6.2 Indication for intervention

Overall, most cases that were treated with "DCB-only" PCI presented as ACS, with an even distribution between NSTEMI, STEMI and unstable angina between the two groups. Significantly more diabetic patients had angiographically established triple vessel disease (diabetics 68% vs nondiabetics 40% $p<0.001$) at the time of intervention, while the opposite was true for non-diabetics who had significantly more single vessel disease prevalent. As discussed before, silent myocardial ischemia or atypical symptoms of CAD are more common in diabetic patients, making it more difficult to identify CAD, delaying diagnosis, treatment and worsening prognosis (10). Furthermore, diabetic patients are at increased risk for widespread atherosclerotic disease and more frequent complex coronary artery disease (6,56,57). Triple vessel disease has been associated with higher rates of TLR in both diabetics and non-diabetics after PCI (12,58) and could have contributed to the higher rates of TLR in our diabetic group.

6.3 Angiographic findings and vessel characteristics

Angiographic findings were similar in both cohorts, with no significant differences present when comparing the initial percentage of stenosis and characteristics of the DCBs deployed. In most cases, the percentage of initial vessel stenosis was between 90-99%. The vessels on which the DCBs were most commonly deployed were the first obtuse marginal branch of the left circumflex artery and the first diagonal branch of the left anterior descending artery. The average diameter of DCBs deployed was 2.47 mm (CI 95% 2.41-2.53). We used this parameter to approximate the average vessel size that the DCBs were most commonly employed in. The small mean diameter of DCB used and the vessels they were most commonly deployed in demonstrates that a majority of treated lesions were located in small coronary arteries. As discussed previously, multiple studies have demonstrated the noninferiority of using DCBs to DES in treatment of de novo SVD. Small vessel coronary artery disease is highly prevalent in the diabetic population and has been a contributor to worse outcomes PCI outcomes due to higher rates of ISR (59). However, it is interesting to note that the average diameter of DCBs used was larger among the patients in the diabetic group, but the standard deviation also covered a broader range so higher variability of DCB size could have accounted for this finding.

6.4 Complications and post-procedural findings

The rates of post-DCB residual stenosis were also similar, with most cases having excellent angiographic results of <20% residual stenosis (diabetics 52% vs non-diabetics 56%). The overall rate of complications was 4.9%, with no significance between the two groups and with vessel dissection and stent bail out being the two most common complications. The number of cases in which these complications occurred were similar as stent implantation is used for

treatment of iatrogenic vessel dissection (60). There were no cases of acute or subacute vessel thrombosis. A benefit of DCB treatment is the apparent low rates of early vessel thrombosis after deployment. Early outcomes of DCBs were similar between the two groups with no statistical differences, demonstrating that early results of DCB deployment were comparable and satisfactory between both groups.

6.5 Angiographic and Clinical Follow-up

The mean clinical follow-up for patients in our study was 30.6 months, with no significant difference between the two groups. However, diabetic patients had higher rates of angiographic follow-up. We further divided angiographic follow-up into elective angiographic follow-up or repeat PCI due to new ACS. As mentioned earlier the rates of ACS were not significant between the two groups, but the rate of elective PCI was significantly higher among the diabetic group (diabetics 59.3% vs non-diabetics 31.9%, $p<0.001$). Operators could have chosen to follow-up on diabetic patients more vigilantly considering it is well established that they have higher rates of complications post-PCI. It is also possible that patients in this group were more often scheduled for repeat PCI for a different lesion, considering that more patients in this group had multi-vessel disease.

6.6 Primary End-Points

Out of our primary endpoints, only TLR was found to be significantly different between the two groups. It is important to note that one case of TLR that occurred in the diabetic group occurred in a patient who because of vessel dissection was treated with stent bail out. Both re-hospitalization and new ACS rates between diabetics and non-diabetics did not reach statistical significance but were higher in the diabetic group. The rate of TLR was higher in

patients who presented with ACS (31.3% of all TLR). When comparing with their respective groups 5.1% of TLR in diabetics occurred in ACS and 13.6% during an elective procedure. However, it is important to note that 42.9% of diabetic patients had ACS due to TLR.

These rates were definitively lower among the non-diabetic group, with 3.0% for the former and 1.8% in the latter. Regardless, of the TLR accounting for 42.9% of ACS cases in diabetics and 28.6% of cases in non-diabetics, ACS did not reach clinical significance. The rate of TLR in elective follow-up angiography was lower in both groups, but when comparing TLR in ACS versus TLR in elective angiography, there was overall more TLR during elective procedures. Ultimately, the finding of significant rates of TLR among diabetics without worsening MACE has been reflected in trials that compared the usage of DES to CABG in diabetics (14).

Botey et al, in their prospective study demonstrated a similar finding to our study's; at 12 months follow-up, diabetics similarly had significantly higher rates of TLR (2% vs 0,5% $p<0.014$), while rates of MACE were higher in the diabetic arm but did not reach statistical significance (61). The rate of TLR among diabetics in Botey's study was similar to rates of TLR in diabetics reported in the BASKET-SMALL 2 and BELLO trial (45,50). Our findings of TLR were much higher among diabetic patients at 18,6%. However, the findings in these other studies reflect follow-up rates after 12 months, while patients included in our study had in some case much longer time to follow-up (mean follow up for diabetics was 30 months).

Our result suggests that diabetes is a predictor of worse outcome in "DCB-only" angioplasty. The similar indications for intervention and post-procedural outcomes indicate that these variables likely did not contribute to worse PCI outcomes. The sociodemographic findings amongst the diabetics included many risk factors for worse PCI outcomes, these risk factors are more prevalent among diabetic patients and likely have historically contributed to the worse PCI

outcomes in this population. MACE was also not significantly different between the two groups, however; rates of new ACS and re-hospitalization were still higher among the diabetic group. Based on the results of our study, diabetes seems to be a predictor of worse outcome after DCB treatment, but does not render it unsafe for usage. Further prospective studies need to be done on the use of DCBs in diabetic patients to further establish the risks and outcomes in this population.

6.7 Study Limitations

Our study is limited by the fact that all data was retrospectively collected and analyzed and it is limited to one hospital center. Our study population was also small with ultimately a small percentage of diabetics compared to the overall study population. Also, while we investigated the rates of TLR among diabetics our only time criteria were that patients need to have at least 6 months follow-up with no definite end point. We also only collected data on how many months after there was clinical follow-up, not months to angiographic follow-up. For further investigation, vessel diameters and lesion lengths should be measured and not approximated from data about the DCBs themselves.

7. CONCLUSIONS

1. "DCB-only" PCI for de novo coronary artery lesions is a potential safe alternative to DES in diabetic patients even though it is similarly associated with significantly higher rates of TLR (diabetics 19% vs nondiabetics 3% $p<0.001$). Rates of re-hospitalization and new ACS did not reach statistical significance.
2. Diabetic patients exhibited significantly higher rates of arterial hypertension ($p<0.001$), higher BMI ($p<0.005$) and had higher rates of previous myocardial infarction ($p<0.038$).
3. Pre-procedural angiographic and vessel characteristics were similar between two groups, with the exception of a significantly higher rate of triple vessel disease among the diabetic group (diabetics 68% vs nondiabetics 40% $p<0.001$).
4. Procedural complications were similar among diabetics and non-diabetics and early procedural outcomes also showed no statistical differences among the groups.
5. Clinical follow-up was similar between the two groups, while significantly more diabetic patients received angiographic follow-up (64.4% vs 34.9%, $p<0.001$).
6. Diabetics patients had significantly higher rates of elective angiographic follow-up (59.3% vs 31.9%, $p<0.001$); however angiographic follow-up due to new ACS was not statistically significant between the two groups.
7. ACS due to TLR occurred at a rate of 5.1% in diabetics and accounted for 42.9% of overall ACS in the diabetic group.
8. This is a retrospective study, further investigation of "DCB-only" PCI in de novo coronary artery disease in diabetics should be investigated via prospective observational and randomized control trials to establish whether they are truly a suitable alternative to DES.

8. ACKNOWLEDGEMENTS

I would like to give special thanks to my mentor, Assistant Professor Kristina Marić-Besić, for giving me this opportunity and for being a constant guide and support during the process. Thank you for the knowledge that you have bestowed on me.

Special thanks, to Dr. Hrvoje Barić, for helping me with the statistical data analysis, I could not have done it without you.

And last, but not least, a special thank you to my friends and family for tirelessly supporting over the last six years.

9. REFERENCES

1. Anderson JL. 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. Vol. 127, Circulation. 2013.
2. Ibanez B, James S. The 2017 ESC STEMI Guidelines. Eur Heart J. 2018 Jan 7;39(2):79–82.
3. Fam J, Khoo C, Lau Y, Lye W, Cai X, Choong L, et al. Age and diabetes mellitus associated with worse outcomes after percutaneous coronary intervention in a multi-ethnic Asian dialysis patient population. Singapore Med J. 2021 Jun;62(6):300–4.
4. Bernelli C, Chan J, Chieffo A. Drug-eluting stent outcomes in diabetes. Vol. 12, Expert Review of Cardiovascular Therapy. 2014. p. 95–109.
5. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part i. Vol. 34, European Heart Journal. 2013. p. 2436–46.
6. Hurst RT, Lee RW. Increased Incidence of Coronary Atherosclerosis in Type 2 Diabetes Mellitus: Mechanisms and Management [Internet]. 2003. Available from: www.annals.org
7. Mercado N, Boersma E, Wijns W, Gersh BJ, Morillo CA, De Valk V, et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: A comparative analysis from the balloon-to-stent era. J Am Coll Cardiol. 2001 Sep 1;38(3):645–52.
8. Abacı A, Og A, Kahraman S, Kemal Eryol N, Arınç H, Ergin A. Effect of Diabetes Mellitus on Formation of Coronary Collateral Vessels [Internet]. 1999. Available from: http://www.circulationaha.org
9. Ishio N, Kobayashi Y, Iwata Y, Kitahara H, Fukushima K, Asano T, et al. Ubiquitous atherosclerosis in coronary arteries without angiographically significant stenosis. Heart Vessels. 2010 Jan;25(1):27–34.
10. Tavares CAF, Wajchjenberg BL, Rochitte C, Lerario AC. Screening for asymptomatic coronary artery disease in patients with type 2 diabetes mellitus. Vol. 60, Archives of Endocrinology and Metabolism. Sociedade Brasileira de Endocrinologia e Metabologia; 2016. p. 143–51.

11. Mehran R, Dangas GD, Kobayashi Y, Lansky AJ, Mintz GS, Aymong ED, et al. Short- and long-term results after multivessel stenting in diabetic patients. J Am Coll Cardiol. 2004 Apr 21;43(8):1348–54.

12. Thuijs DJFM, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. The Lancet. 2019 Oct 12;394(10206):1325–34.

13. Stefanini GG, Baber U, Windecker S, Morice MC, Sartori S, Leon MB, et al. Safety and effi cacy of drug-eluting stents in women: A patient-level pooled analysis of randomised trials. The Lancet. 2013;382(9908):1879–88.

14. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, et al. Randomized Comparison of Percutaneous Coronary Intervention With Coronary Artery Bypass Grafting in Diabetic Patients: 1-Year Results of the CARDia (Coronary Artery Revascularization in Diabetes) Trial. J Am Coll Cardiol. 2010 Feb 2;55(5):432–40.

15. Goel SS, Shishehbor MH. Strategies for multivessel revascularization in patients with diabetes. Vol. 29, Cardiology Review. 2013.

16. McKavanagh P, Zawadowski G, Ahmed N, Kutryk M. The evolution of coronary stents. Vol. 16, Expert Review of Cardiovascular Therapy. Taylor and Francis Ltd; 2018. p. 219–28.

17. nejm199408253310802.

18. nejm199408253310801.

19. Pendyala LK, Yin X, Li J, Chen JP, Chronos N, Hou D. The First-Generation Drug-Eluting Stents and Coronary Endothelial Dysfunction. 2009.

20. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbæk H, et al. Analysis of 14 Trials Comparing Sirolimus-Eluting Stents with Bare-Metal Stents. New England Journal of Medicine. 2007 Mar 8;356(10):1030–9.

21. Joner M, Finn A V., Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of Drug-Eluting Stents in Humans: Delayed Healing and Late Thrombotic Risk. J Am Coll Cardiol. 2006 Jul 4;48(1):193–202.

22. Navarese EP, Kowalewski M, Kandzari D, Lansky A, Górny B, Kołtowski Ł, et al. First-generation versus second-generation drug-eluting stents in current clinical practice: Updated evidence from a comprehensive meta-analysis of randomised clinical trials comprising 31 379 patients. Open Heart. 2014;1(1).

23. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, et al. Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis. J Am Coll Cardiol. 2015 Jun 16;65(23):2496–507.

24. Gao L, Chen YD. Application of drug-coated balloon in coronary artery intervention: Challenges and opportunities. Vol. 13, Journal of Geriatric Cardiology. Science Press; 2016. p. 906–13.

25. Nestelberger T, Kaiser C, Jeger R. Drug-coated balloons in cardiovascular disease: benefits, challenges, and clinical applications. Vol. 17, Expert Opinion on Drug Delivery. Taylor and Francis Ltd; 2020. p. 201–11.

26. Liu C, Wolfers M, Awan BEZ, Ali I, Lorenzana AM, Smith Q, et al. Drug-coated balloon versus plain balloon angioplasty for hemodialysis dysfunction: A meta-analysis of randomized controlled trials. J Am Heart Assoc. 2021 Dec 7;10(23).

27. Sato Y, Kuntz SH, Surve D, Jinnouchi H, Sakamoto A, Cornelissen A, et al. What are the Pathological Concerns and Limitations of Current Drug-coated Balloon Technology? Heart Int. 2019;13(1):15.

28. Jeger R V., Eccleshall S, Wan Ahmad WA, Ge J, Poerner TC, Shin ES, et al. Drug-Coated Balloons for Coronary Artery Disease: Third Report of the International DCB Consensus Group. Vol. 13, JACC: Cardiovascular Interventions. Elsevier Inc.; 2020. p. 1391–402.

29. Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, et al. A Randomized, Multicenter, Single-Blinded Trial Comparing Paclitaxel-Coated Balloon Angioplasty With Plain Balloon Angioplasty in Drug-Eluting Stent Restenosis: The PEPCAD-DES Study. J Am Coll Cardiol. 2012 Apr 10;59(15):1377–82.

30. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García Del Blanco B, Seidelberger B, Iñiguez A, et al. A Randomized Comparison of Drug-Eluting Balloon Versus Everolimus-Eluting Stent in Patients With Bare-Metal Stent–In-Stent Restenosis: The RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs. Everolimus-eluting Stent). J Am Coll Cardiol. 2014 Apr 15;63(14):1378–86.

31. Nestelberger T, Kaiser C, Jeger R. Drug-coated balloons in cardiovascular disease: benefits, challenges, and clinical applications. Vol. 17, Expert Opinion on Drug Delivery. Taylor and Francis Ltd; 2020. p. 201–11.

32. Shlofmitz E, Iantorno M, Waksman R. Restenosis of Drug-Eluting Stents: A New Classification System Based on Disease Mechanism to Guide Treatment and State-of-The-Art Review. Vol. 12, Circulation: Cardiovascular Interventions. Lippincott Williams and Wilkins; 2019.

33. Dash D. To cite: Dash D. Heart Asia [Internet]. 2014;6:18–25. Available from: http://heartasia.bmj.com/

34. Kleber FX, Rittger H, Ludwig J, Schulz A, Mathey DG, Boxberger M, et al. Drug eluting balloons as stand alone procedure for coronary bifurcational lesions: results of the randomized multicenter PEPCAD-BIF trial. Clinical Research in Cardiology. 2016 Jul 14;105(7):613–21.

35. Stella PR, Belkacemi A, Dubois C, Nathoe H, Dens J, Naber C, et al. A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: Six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. Catheterization and Cardiovascular Interventions. 2012 Dec 1;80(7):1138–46.

36. Bruch L, Zadura M, Waliszewski M, Platonic Z, Eränen J, Scheller B, et al. Results From the International Drug Coated Balloon Registry for the Treatment of Bifurcations. Can a Bifurcation Be Treated Without Stents? J Interv Cardiol. 2016 Aug;29(4):348–56.

37. Corballis NH, Paddock S, Gunawardena T, Merinopoulos I, Vassiliou VS, Eccleshall SC. Drug coated balloons for coronary artery bifurcation lesions: A systematic review and focused meta-analysis. PLoS One. 2021 Jul 9;16(7):e0251986.

38. Wybraniec MT, Bańka P, Bochenek T, Roleder T, Mizia-Stec K. Small vessel coronary artery disease: How small can we go with myocardial revascularization? Vol. 28, Cardiology Journal. Via Medica; 2021. p. 767–78.

39. Biondi-Zoccai G, Moretti C, Abbate A, Sheiban I. Percutaneous coronary intervention for small vessel coronary artery disease. Cardiovascular Revascularization Medicine. 2010 Jul 1;11(3):189–98.

40. Cortese B, Micheli A, Picchi A, Coppolaro A, Bandinelli L, Severi S, et al. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. Heart. 2010 Aug;96(16):1291–6.

41. Mohiaddin Tamar F K Wong Anne Burke-Gaffney Richard G Bogle HD. Drug-Coated Balloon-Only Percutaneous Coronary Intervention for the Treatment of De Novo Coronary Artery Disease: A Systematic Review. Available from: https://doi.org/10.6084/

42. Qian J, Wu Y, Li C, Yin J, Fu G, Wang J, et al. Drug‐coated balloon for the treatment of small vessel disease: 9 months of angiographic results and 12 months of clinical outcomes of the PEPCAD China SVD study. Catheterization and Cardiovascular Interventions. 2023 Jan 8;101(1):33–43.

43. Jeger R V., Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Leibundgut G, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. The Lancet. 2018 Sep 8;392(10150):849–56.

44. Jeger R V., Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Weilenmann D, et al. Long-term efficacy and safety of drug-coated balloons versus drug-eluting stents for small coronary artery disease (BASKET-SMALL 2): 3-year follow-up of a randomised, non-inferiority trial. The Lancet. 2020 Nov 7;396(10261):1504–10.

45. Latib A, Colombo A, Castriota F, Micari A, Cremonesi A, De Felice F, et al. A Randomized Multicenter Study Comparing a Paclitaxel Drug-Eluting Balloon With a Paclitaxel-Eluting Stent in Small Coronary Vessels: The BELLO (Balloon Elution and Late Loss Optimization) Study. J Am Coll Cardiol. 2012 Dec 18;60(24):2473–80.

46. Mangner N, Farah A, Ohlow MA, Möbius-Winkler S, Weilenmann D, Wöhrle J, et al. Safety and Efficacy of Drug-Coated Balloons Versus Drug-Eluting Stents in Acute Coronary Syndromes: A Prespecified Analysis of BASKET-SMALL 2. Circ Cardiovasc Interv. 2022 Feb 1;15(2):e011325.

47. Scheller B, Ohlow MA, Ewen S, Kische S, Rudolph TK, Clever YP, et al. Bare metal or drug-eluting stent versus drug-coated balloon in non-ST-elevation myocardial infarction: The randomised PEPCAD NSTEMI trial. EuroIntervention. 2020 Apr 1;15(17):1527–33.

48. Niehe SR, Vos NS, Van Der Schaaf RJ, Amoroso G, Herrman JPR, Patterson MS, et al. Two-Year Clinical Outcomes of the REVELATION Study: Sustained Safety and Feasibility of Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction. J Invasive Cardiol. 2022 Jan;34(1):E39–42.

49. Lee CW, Park DW, Lee BK, Kim YH, Hong MK, Kim JJ, et al. Predictors of Restenosis After Placement of Drug-Eluting Stents in One or More Coronary Arteries. Am J Cardiol. 2006 Feb;97(4):506–11.

50. Wöhrle J, Scheller B, Seeger J, Farah A, Ohlow MA, Mangner N, et al. Impact of Diabetes on Outcome With Drug-Coated Balloons Versus Drug-Eluting Stents: The BASKET-SMALL 2 Trial. JACC Cardiovasc Interv. 2021 Aug 23;14(16):1789–98.

51. Weber T, Lang I, Zweiker R, Horn S, Wenzel RR, Watschinger B, et al. Hypertension and coronary artery disease: epidemiology, physiology, effects of treatment, and recommendations: A joint scientific statement from the Austrian Society of Cardiology and the Austrian Society of Hypertension. Wien Klin Wochenschr. 2016 Jul 1;128(13–14):467–79.

52. Singh M, Gersh BJ, McClelland RL, Ho KKL, Willerson JT, Penny WF, et al. Predictive factors for ischemic target vessel revascularization in the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial. J Am Coll Cardiol. 2005 Jan 18;45(2):198–203.

53. Zibaeenezhad MJ, Mohammadi SS, Sayadi M, Khorshidi S, Bahramali E, Razeghian-Jahromi I. The impact of diabetes mellitus and hypertension on clinical outcomes in a population of Iranian patients who underwent percutaneous coronary intervention: A retrospective cohort study. J Clin Hypertens. 2019 Nov 1;21(11):1647–53.

54. Khera A V., Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018 Sep 13;50(9):1219–24.

55. Gray N, Picone G, Sloan F, Yashkin A. Relation between BMI and diabetes mellitus and its complications among US older adults. South Med J. 2015;108(1):29–36.

56. Burgess SN, Mussap CJ, French JK. Management of Acute Coronary Syndromes in Patients with Diabetes: Implications of the FREEDOM Trial. Vol. 35, Clinical Therapeutics. 2013. p. 1069–75.

57. Naito R, Miyauchi K. Coronary Artery Disease and Type 2 Diabetes Mellitus Current Treatment Strategies and Future Perspective. 2017.

58. Hata R, Kubo S, Tsuneyoshi H, Shimamoto T, Kuwayama A, Ohya M, et al. Long-term outcomes of three-vessel coronary artery disease after coronary revascularization by percutaneous coronary intervention using second-generation drug-eluting stents versus coronary artery bypass graft surgery. Cardiovasc Interv Ther. 2020 Apr 10;35(2):194–202.

59. Akiyama T, Moussa I, Reimers B, Ferraro M, Kobayashi Y, Blengino S, et al. Angiographic and clinical outcome following coronary stenting of small vessels: A comparison with coronary stenting of large vessels. J Am Coll Cardiol. 1998 Nov 15;32(6):1610–8.

60. Al-Lamee R, Ielasi A, Latib A, Godino C, Ferraro M, Mussardo M, et al. Incidence, Predictors, Management, Immediate and Long-Term Outcomes Following Grade III Coronary Perforation. JACC Cardiovasc Interv. 2011 Jan 1;4(1):87–95.

61. Benjamin BK, Lu W, Han Z, Pan L, Wang X, Qin X, et al. Drug-Coated Balloon-Only Angioplasty Outcomes in Diabetic and Nondiabetic Patients with de Novo Small Coronary Vessels Disease. J Interv Cardiol. 2021;2021.

10.BIOGRAPHY

Zoya Jelovecki-Dokic was born on May 11th 1999 in New York City, New York. She is a first generation American, her parents are from Zagreb, Croatia. Zoya graduated from Ithaca High School in June 2016, one year prior to her expected graduation date and enrolled in the University of Zagreb Medical School Medical Studies in English in July 2017. She decided to pursue her medical degree in Croatia due to her Croatian heritage.

Since enrolling in the medical school, Zoya has been involved in multiple extracircular activities. She was a student demonstrator at the department of anatomy for two years and at the department of internal medicine for two years. She served as the student representative for the international students in both the Croatian Student Council and eMED, the medical student council of the MSE program. She was a member of the Croatian Student Summit Organizing

Committee multiple years in a row and has also been an active participant in multiple congress where she has presented her scientific work.

Zoya's primary interest in medicine is the field of cardiology and she hopes to one day pursue a residency in this field. Within in the field of cardiology her primary interest is interventional cardiology. In her free time Zoya likes to exercise, read books, knit and do yoga.