RISK FACTOR DISTRIBUTION AND LONG-TERM OUTCOMES IN YOUNG PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION IN MACEDONIA

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SUMMARY – The aim was to assess coronary artery disease (CAD) risk factor distribution and long-term outcomes in young patients undergoing percutaneous coronary intervention (PCI) in Macedonia. A total of 12,361 PCI patients (from March 2011 to December 2017) were included in the study. Group 1 included 309 young patients aged ≤40 as the main study group, comparing them to 12,052 older PCI patients (group 2) during the study period. We compared CAD risk factor distribution, clinical and procedure characteristics. Additionally, angiographic data, long-term major adverse cardiac and cerebrovascular events (MACCE) and mortality were analyzed in group 1 patients. Median age was 36±4 years in group 1 and 62±11 years in group 2. Male patients predominated in both groups (88% *vs.*73%). Positive family history for CAD, smoking and obesity was much more common in the young group (p<0.0001). ST segment elevation myocardial infarction (STEMI) primary PCI was also more frequent with 48% of PCI in the young group (p<0.0001). Multivessel CAD and chronic total occlusion interventions were more common in the older group (51% and 28%, respectively; p<0.0001). Procedure duration (31±0.4 *vs.* 35±22 min) and fluoroscopy time (9±4 *vs.* 9±12 min) were similar in both groups. There was no difference in access site bleeding (4.8% *vs.* 4.3%). During the 3.5-year median follow up, MACCE was present in 1.9% of young patients. In conclusion, positive family history for CAD, obesity and smoking were the most common risk factors in the young PCI population. Young PCI patients usually had single vessel CAD with STEMI being more frequent as the cause for primary PCI. Long-term annual survival exceeded 99% in these patients with excellent prognosis after PCI.

Key words: *Coronary artery disease; Risk factors; Percutaneous coronary intervention; ST elevation myocardial infarction*

Introduction

Coronary artery disease (CAD) is one of the most common causes of morbidity and mortality in the world population. CAD is most common in the elderly population and rarely occurs in people under 40 years. However, recent studies have shown that ever more young people develop CAD at an early age, most commonly due to their unhealthy lifestyle, stress and development of metabolic syndrome[1-4].

Other studies have reported that risk factor presence, CAD presentation and angiographic data differ in the young compared to the old population[5]. Identifying risk factors that are most common in young people with CAD and understanding the process of atherosclerosis causing significant CAD in this population can help in prevention and decreasing the number of young CAD patients.

Furthermore, angiographic, clinical and risk factor evaluation of CAD in the young population can contribute to determination of future prognosis and life expectancy in these patients.

In this study, we aimed to assess cardiovascular risk factor distribution, clinical and procedure characteristics in patients less than 40 years of age undergoing percutaneous coronary intervention (PCI) and compare these data with those on PCI patients older than 40 years. Additionally, angiographic data, major adverse cardiac and cerebrovascular events (MACCE) and mortality were analyzed in the young group with median follow up of 3.5 years (41.4 months, 20-60 IQR).

Materials and Methods

Patient population

This was a retrospective single center study including 12,361 PCI patients over a 7-year period (March 2011 to December 2017) referred for PCI to a large volume tertiary referral center. The group of young patients aged ≤40 was the main study group (group 1). This group was compared to the group of older PCI patients (group 2) during the same period. Patients with previous PCI and myocardial infarction (MI) were excluded from the study (53 in group 1 and 5319 in group 2), so as not to have any confounding factors on group comparison. All included patients had *de novo* diagnosis of CAD and first time PCI.

Almost all procedures (99%) were performed by transradial access (TRA) and experienced transradial operators with >500 diagnostic TRA procedures and >300 PCI procedures *per* year.

Procedure

Radial artery puncture and cannulation was performed using counter puncture technique with a 20 G plastic intravenous cannula and 0.025 inch mini guidewire of 45 cm, followed by 5 Fr or 6 Fr hydrophilic introducer sheath (Terumo, Japan) placement. Spasmolytic cocktail (verapamil 5 mg) was given intra-arterially through the radial sheath.

Pre-procedural retrograde radial arteriography was performed in all patients to define the radial artery anatomy from mid forearm to ulnobrachial anastomosis and to delineate ulnar artery anatomy as well, thus generating the access roadmap[6-10].

All patients were pretreated with a loading dose of aspirin and clopidogrel 600 mg. After TRA sheath insertion, an initial bolus of 100 IU/kg of unfractionated heparin was administered intravenously.

Post-procedure management: the sheath was removed immediately after the procedure, regardless of the level of anticoagulation, and a compressive dressing or TR band (Terumo, Japan) was applied to the wrist. In order to decrease the rate of radial artery occlusion, we applied patent hemostasis by using pulse oximetry to confirm hemoglobin oxygen saturation on the punctured radial artery (>90%) after hemostasis had been obtained (during measurement, ulnar artery was compressed manually)[11]. Compression was applied for approximately 3-hour period with gradual deflation of the TR band after the 1st hour.

Definitions

Procedure time was defined as the time from puncture until completion of the procedure. Vascular access site complications were defined as the occurrence of an aneurysm, fistula, hematoma, loss of radial pulse, or radial nerve injury.

Access hematoma was classified into five grades according to EASY score (grade I: local hematoma, superficial <5 cm; grade II: hematoma with moderate muscular infiltration; grade III: forearm hematoma and muscular infiltration, below the elbow; grade IV: hematoma and muscular infiltration extending above the elbow; and grade V: ischemic threat – compartment syndrome)[12].

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as mean ± SD, or median (interquartile range). Statistical analysis was performed with JMP 11.O for Windows (SAS Inc., Cary, NC, USA).

Results

We compared 309 young PCI patients (aged ≤40) in group 1 and 12,052 PCI patients (aged >40) in group 2. Median age was 36±4 and 62±11 years in group 1 and 2, respectively. Male patients predominated in both groups (88% and 73%, respectively). Considering cardiovascular risk factor distribution,

Table 1. Risk factor distribution in study population

Clinical variable	PCI patients aged <40 (N=309)	PCI patients aged >40 (N=12,052)	p value
Age (years)	36.7±3.7 (18-40)	62±11 (41-93)	
Male	273 (88%)	8782 (73%)	0.0527
BMI (kg/m²)	**30 (19-47)**	26 (19-52)	**<0.0001**
CAD risk factors			
Hypertension	103 (33%)	**6432 (53%)**	**<0.0001**
Diabetes mellitus	31 (10%)	**2560 (21%)**	**<0.0001**
Dyslipidemia	62 (20%)	3120 (26%)	0.1560
Smoking	**209 (67%)**	2484 (20%)	**<0.0001**
Positive family history for CAD	**129 (21%)**	788 (6.5%)	**<0.0001**

PCI = percutaneous coronary intervention; BMI = body mass index; CAD = coronary artery disease
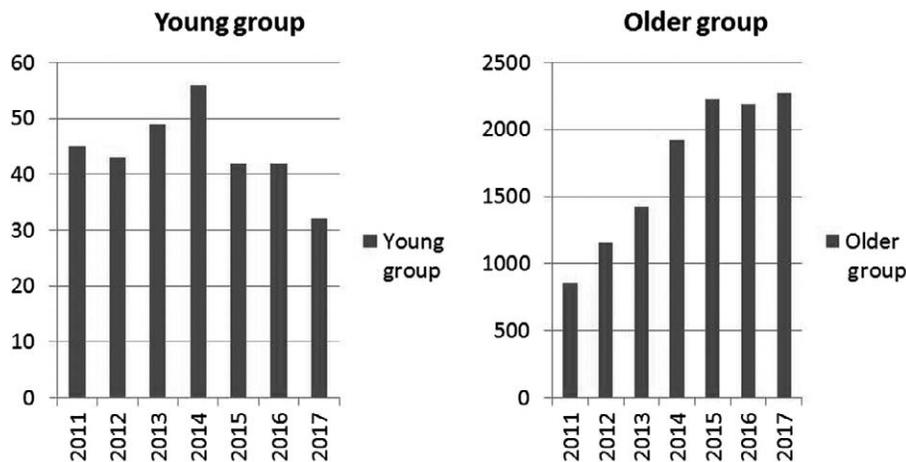

Fig. 1. Distribution of patients undergoing percutaneous coronary intervention according to years.

positive family history of CAD, smoking and obesity were much more common in the young group as compared with the older group (p<0.0001). On the other hand, hypertension and diabetes were much more frequent in the older group (53% *vs.* 33% and 21% *vs.* 10%, respectively) (Table 1).

The group of young patients had primary PCI for ST segment elevation myocardial infarction (STEMI) more often than the older group (48% *vs.* 35% of PCI interventions; p<0.0001). Single vessel CAD was more common in the young group (63%), whereas multivessel CAD and chronic total occlusion interventions were more common in the older group (51% and 28%, respectively; p<0.0001). The rate of PCI in the left main coronary branch (LMN) was similar in groups 1 and 2 (2.2% *vs.* 2.9 %, respectively).

The number of young PCI patients was similar in all consecutive years analyzed in the study, with the lowest number recorded in 2017 (n=32), as opposed to the older PCI patients whose number increased over years from 857 in 2011 to 2269 patients in 2017 (Fig. 1).

Procedure duration (31±0.4 *vs.* 35±22 minutes), contrast volume (120±33 *vs.* 110±35 mL) and fluoroscopy time (9±4 *vs.* 9±12 minutes) were similar in both groups. Ninety-nine percent of all interventions were performed by radial approach. In the young group, all PCI interventions were performed by wrist approach with 95% radial access (TRA) and 5% ulnar access

Table 2. Procedural characteristics of study population

Procedural variable (2011-2017)	N=309	N=12,052	p value
Procedure PCI	160 (52%)	7864(65%)	0.0520
PPCI	**149 (48%)**	4188 (35%)	**<0.0001**
PCI in LM	7 (2.2%)	358 (2.9%)	0.7250
CTO PCI	30 (10%)	**3502 (28%)**	**<0.0001**
Single vessel CAD	**228 (63%)**	5886 (49%)	**<0.0001**
Multi vessel CAD	114 (37%)	**6166 (51%)**	**<0.0001**
Sheath size 5F	32 (10%)	1050 (8.7%)	0.6527
6F	277 (90%)	11002 (91.3%)	0.6527
Fluoroscopy time (min)	9 (1-64)	9 (1-90)	0.9643
Procedural time (min)	31±0.4	35±22	0.0823
Access site bleeding complications	15 (4.8%)	523 (4.3%)	0.9402
Hematoma grade 4/5	1 (0.3%)	29 (0.24%)	
Clinical RA spasm	9 (2.9%)	**490 (4.0%)**	**<0.0001**
Length of stay <2 days	123 (40%)	5290 (44%)	0.3420
Same day discharge	20 (6.4%)	906 (7.5%)	0.6527

PCI = percutaneous coronary intervention; PPCI = primary PCI; CTO = chronic total occlusion; CAD = coronary artery disease; LM = left main; RA = radial artery

(TUA). In the older group, 99.8% of interventions were performed by wrist approach with 97.7% TRA and 2.1% TUA. Access site bleeding complications were similar in both groups (4.8% *vs.* 4.3%), with radial artery spasm being higher in group 2 (4.0% *vs.* 2.9%; p<0.0001). The length of hospital stay was similar in both groups (<2 days in 40% and 44%, respectively) (Table 2).

Angiographic data assessment was performed on all PCI interventions in group 1. Anterior STEMI with left anterior descendant artery (LAD) as culprit was most common presentation in the young STEMI group (48%). Inferior MI with right coronary artery
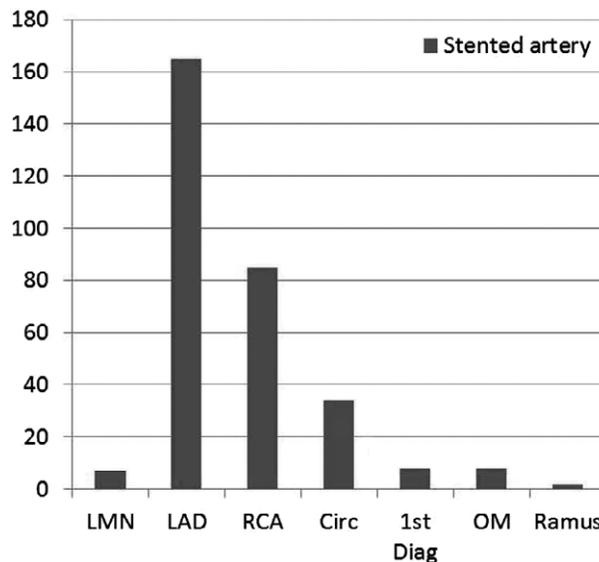

Fig. 2. Stented artery on primary intervention in young patients.

LMN = left main artery; LAD = left anterior descending artery; RCA = right coronary artery; CIRC = circumflex artery, 1st OM = obtuse marginal branch;, 1st Diag = diagonal artery

Table 3. Long-term clinical follow up: MACCE and mortality in the group of young patients

MACCE and mortality	n (%)
Myocardial infarction	5 (1.6)
Cerebrovascular insult	0
Target vessel revascularization	8 (2.5)
Death	1 (0.3)
Major vascular complications	1 (0.3)
Access site bleeding complications	15 (4.8)
Sign of hand ischemia	0
Median follow up	41 months (44 IQR)

MACCE = major adverse cardiac and cerebrovascular events

(RCA) as culprit was present in 19% of STEMI interventions.

In overall PCI interventions in the young group, first time PCI was most commonly performed on the LAD (53%), followed by RCA (27%) and circumflex artery (11%) (Fig. 2).

During the 3.5-year median follow up (41 months, 20-40 IQR), MACCE was present in 1.9% of group 1 patients. Of these, 1.6% had MI and death rate was

0.3% in overall follow up. Only one patient with LMN disease died during hospital stay. Target vessel revascularization occurred in 2.5% of patients at final follow up (Table 3).

Discussion

In this study, we analyzed the characteristics of all young consecutive PCI patients aged ≤40 treated during a 7-year period and compared these data with those on older PCI population in the same period. By comparing these two groups of PCI patients, we aimed to evaluate differences that could identify the risk factors for CAD in young patients in our country and help us improve CAD prevention in the young.

In the young population, CAD is becoming ever more common worldwide and published studies can help define the risk factors and prevent CAD[1,2,5].

Studies involving this population are usually single center studies without enough data from prospective multicenter studies[13,14]. The advantage of our study was that it reflected real life data and clinical practice in the young PCI population in Macedonia over 7 years with long-term follow up.

Our results showed that the risk factor distribution in the young population of PCI patients consisted of positive family history, smoking and obesity that were much more common as compared with the older group population. Furthermore, first time presentation also differed considerably, with a greater number of STEMI presentations in almost half of the patients in the young group. Single vessel CAD was most common in this group, with LAD as the most common artery stented. The number of young PCI patients in our population was consistent over years, as opposed to the older PCI population whose number grew and reached highest figure in 2017. This was most probably due to the aging of the population and ever more elderly patients being referred for PCI as opposed to earlier years. Advances in PCI technology and techniques over the past decade had also led to improving outcomes and lowering complication rates in the otherwise complicated PCI patient group. Consistency in the number of younger PCI patients was comparable to other published studies[1-2,5,14-19], but we think that this value is underestimated due to the late detection of CAD in young patients with common multi-vessel disease in their early forties. A speedy cardiovascular

diagnosis and treatment[20] is necessary for early detection and treatment of young CAD patients. In addition, a good primary prevention program is needed to further decrease this number at the national level.

The survival rate in our young PCI population was 99.7% at 3.5-year median clinical follow up, with excellent prognosis and low rate of MACCE. Our findings are similar to other previously published studies[5,15-19], but also present the first time published data from our country.

It is important to note that primary PCI strategy in STEMI is the default strategy in our country with <1% of patients undergoing fibrinolysis during STEMI. Our hospital is a high volume transradial center (80% of all PCI interventions in the country) and the main referral center for primary PCI and complex procedures. Transradial approach has been the default approach in our center since 2008[21], which is in accordance with the ESC guidelines for treatment of PCI patients[22-24], and most probably has contributed to the low MACCE and mortality in our results[7-9].

Upon analyzing the risk factors in our young PCI population, we can conclude that eliminating smoking, which was present in 67% of the young PCI population as one of the causes of atherosclerosis, can help us significantly in decreasing CAD. We also found that the young PCI group had a medium body mass index 30, indicating that obesity is also a significant risk factor for CAD in the young Macedonian population and that lifestyle modification can also help decrease the number of young CAD patients[25]. Early diagnosis and treatment with regular cardiologic check-ups and elimination of other risk factors are necessary for young patients with strong positive family history of CAD[26].

Study limitations

This was a retrospective study and larger prospective multicenter studies are needed to prove our results. The study produced real life results on all PCI patients included over a 7-year period. We only excluded PCI patients that had previous MI and PCI, to have a more precise analysis of risk factor distribution and comparison between the two groups and to eliminate bias.

Conclusion

Positive family history of CAD, obesity and smoking were the most common risk factors in the young

PCI population. Young PCI patients usually had single vessel CAD, with STEMI being more frequent as the cause for primary PCI. Long-term annual survival was more than 99% in these patients, with excellent prognosis after PCI. Working towards prevention and lifestyle modification can help reduce the number of young patients with CAD.

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Sažetak

DISTRIBUCIJA RIZIČNIH ČIMBENIKA I DUGOROČNI ISHODI U MLADIH BOLESNIKA PODVRGNUTIH PERKUTANOJ KORONARNOJ INTERVENCIJI U MAKEDONIJI

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Cilj istraživanja bio je procijeniti distribuciju rizičnih čimbenika za koronarnu arterijsku bolest (KAB) i dugoročne ishode kod mladih bolesnika podvrgnutih perkutanoj koronarnoj intervenciji (PKI) u Makedoniji. U istraživanje je bilo uključeno ukupno 12.361 bolesnika podvrgnutih PKI (od ožujka 2011. do prosinca 2017. godine). Skupina 1. obuhvatila je 309 mladih bolesnika u dobi od ≤40 godina kao glavna ispitna skupina koja je tijekom istraživanja uspoređena sa skupinom 2. koja je uključivala 12.052 starijih bolesnika. Uspoređivali smo distribuciju rizičnih čimbenika za KAB te kliničke osobine i značajke zahvata. Uz to, u skupini 1. analizirani su angiografski podaci, dugoročni teži štetni srčani i cerebrovaskularni događaji (*major adverse cardiac and cerebrovascular events*, MACCE) i smrtnost. Medijan dobi bio je 36±4 godine u skupini 1. i 62±11 godine u skupini 2. Pozitivna obiteljska anamneza za KAB, pušenje i pretilost bili su znatno češći u mladoj skupini (p<0,0001). Primarna PKI zbog STEMI bila je također češća s 48% PKI u mladoj skupini (p<0,0001). KAB višestrukih krvnih žila i intervencije zbog kronične potpune okluzije bile su češće u starijoj skupini (51% odnosno 28%; p<0,0001). Trajanje zahvata (31±0,4 prema 35±22 min) i fluoroskopije (9±4 prema 9±12 min) bilo je slično u objema skupinama. Nije bilo razlike u krvarenju na ulaznom mjestu (4,8% prema 4,3%). Tijekom medijana praćenja od 3,5 godine MACCE su zabilježeni u 1,9% mladih bolesnika. U zaključku, najčešći čimbenik rizika u populaciji mladih bolesnika podvrgnutih PKI bila je pozitivna obiteljska anamneza za KAB, pretilost i pušenje. Mladi bolesnici uglavnom su imali KAB jedne krvne žile i podvrgnuti su primarnoj PKI zbog STEMI. Dugoročno godišnje preživljenje bilo je više od 99% u ovih bolesnika s izvrsnom prognozom nakon PKI.

Ključne riječi: *Koronarne arterije, bolesti; Rizični čimbenici; Perkutana koronarna intervencija; Infarkt miokarda s elevacijom ST-segmenta*