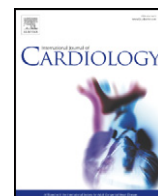




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Early and long-term outlook of percutaneous coronary intervention for bifurcation lesions in young patients[☆]

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ABSTRACT

Background: Coronary artery disease is most common in older patients, but may occur in younger subjects. The outlook of young patients after percutaneous coronary intervention (PCI) of challenging lesion subsets such as coronary bifurcations, is not established. We thus aimed to appraise the early and long-term results of PCI for bifurcations in young patients.

Methods: A multicenter, retrospective study was conducted enrolling consecutive patients undergoing bifurcation PCI between 2002 and 2006 in 22 Italian centers. Patients were divided in 2 groups: age ≤ 45 years, and age > 45 years. The primary end-point was long-term rate of major adverse cardiac events (MACE).

Results: 4,314 patients were included: 195 (4.5%) in the younger group, and 4119 (95.5%) in the older group. 30-day outcomes did not show significant differences in MACE rates, with 1.0% in the ≤ 45 years group and 2.1% in the > 45 years group ($p=0.439$), with death in 0.5% and 1.2% ($p=0.388$). At long-term follow-up (24.4 ± 15.1 months), younger patients showed similar rates of MACE, (12.8% vs. 16.6%, $p=0.161$), myocardial infarction (3.1% vs. 3.7%, $p=0.633$), target lesion revascularization (11.3% vs. 12.5%, $p=0.627$), or stent

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thrombosis (1.5% vs. 2.8%, $p=0.294$), despite an increased risk of death in older patients (1.0% vs. 5.0%, $p=0.012$). Even at extensive multivariable analysis, younger patients still faced a similar risk of MACE (HR=0.78 [0.48–1.27], $p=0.318$).

Conclusions: Despite their low age, young patients undergoing PCI for bifurcation face a significant risk of early and late non-fatal adverse events. Thus, they should not be denied careful medical management and follow-up.

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1. Introduction

Coronary bifurcation lesions still represent a challenge for interventional cardiologists. Even in the modern era, patients undergoing percutaneous coronary interventions (PCI) of bifurcation lesions face lower procedural success, greater complication rates and worse outcome compared with PCI of simple coronary lesions [1,2]. Advanced age has been traditionally identified as an important risk factor for adverse outcome in patients suffering from ischemic heart. Accordingly, older patients treated invasively usually have higher mortality rates, increased bleeding risk, and overall poorer outcomes [3–7].

Since age is a powerful determinant of prognosis, and advanced age is associated with worst results, could young age be related with better outcomes? A small number of trial have addressed this subjects, and even fewer data are available comparing results in different age groups in patients treated invasively for complex coronary lesions. Thus, we sought to determine the impact of young age on short and long-term outcome in patients undergoing PCI for bifurcation coronary lesions. We evaluated the rates of major adverse cardiovascular events (MACE) in patients enrolled in the Italian Multicenter Registry on Bifurcation (I-BIGIS) study, comparing events between subjects younger and older than 45 years.

2. Methods

The I-BIGIS was an Italian multicenter study enrolling consecutive patients undergoing percutaneous coronary bifurcation revascularization between January 2002 and December 2006. It included both elective and urgent admissions. Data collection and study design have been previously described [8,9]. Briefly, patients undergoing percutaneous revascularization at the site of a coronary bifurcation lesion of a major epicardial coronary artery and eligible for 1-year follow-up were included in the study. No specific exclusion criteria were adopted. All analyses were based on the actual procedural technique and implanted stent at the time of enrollment, regardless of previous myocardial revascularization. All patients provided written informed consent for the PCI procedure. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and ethical committee approval was waived given the observational design.

2.1. Study design and data collection

This was a retrospective, observational clinical study sponsored by the Italian Society of Invasive Cardiology (SICI-GISE), where all the Italian catheterization laboratories constituting the SICI-GISE data set providers were invited to join the registry. Laboratories were included if they met the preset minimum requirements (routine performance of PCI, DES availability, and presence of a dedicated procedural database throughout the study period). Data for this study were drawn from a dedicated database. Given the observational and retrospective nature, all procedural aspects were left to center practice. Follow-up was based on hospital charts, direct visits, phone interviews and contacts with referring physicians.

2.2. Clinical outcomes and definitions

Primary end-point of our study was rate of MACE, assessed as the composite of cardiac death, Q wave and non-Q wave myocardial infarction (MI), target lesion revascularization (TLR), and stent thrombosis (ST) at 1 year or at the longest follow-up available. Secondary end-points were short-term (30-day) rate of MACE, and rates of singular adverse events both in short and long term follow-up.

As previously reported [8,10], bifurcation lesions were defined as presence of >50% diameter stenosis in a major epicardial coronary vessel, involving coronary bifurcation. Main vessel diameter had to be between 2.5 and 4.5 mm, while side branch had to be between 2.25 and 4.5 mm. Medina classification [11] was used to define true bifurcation lesions. Procedural success was defined as revascularization success without the occurrence of MACE during in-hospital stay. Cardiac death was defined as any death due to cardiac cause, or procedure-related deaths, and death of unknown cause. Myocardial infarction was defined according to the 2007 consensus statement from the Joint ESC/ACCF/AHA/WHF task force [12]. Target lesion revascularization was defined as any

revascularization procedure performed for angiographic restenosis within 5 mm proximal or distal to the treated lesion, associated with evidence of inducible myocardial ischemia. Stent thrombosis was assessed using the Academic Research Consortium definition [13] as definite, probable, or possible. To avoid any risk of tautology or redundancy, each patient could provide only one hard event per event type.

2.3. Statistical analysis

Baseline characteristics of the patients were summarized with means (standard deviation) for continuous variables and n (%) for discrete variables. Student t and Yates corrected χ^2 tests were used for bivariate analyses. Multivariable Cox proportional hazard analyses (reported as hazard ratio [HR] with 95% confidence intervals) were performed to appraise the association between age group and long-term risk of MACE by adjusting for all covariates significantly ($p<0.05$) associated with young age at bivariate analyses. Computations were performed with SPSS 20 (IBM, Armonk, NY, USA) and 2-tailed p values unadjusted for multiplicity are reported throughout.

3. Results

3.1. Population characteristics

This study comprised a total of 4,314 patients, enrolled between January 2002 and December 2006. The main clinical characteristics are reported in Table 1. As expected, patients ≤ 45 years old represented only a small share of the study population. Mean age in the young group was 41.4, compared with 65.5 in the older group ($p<0.001$).

Cardiovascular risk factors and comorbidities were significantly different between younger and older patients. Specifically, the latter presented higher incidence of diabetes, hypertension and chronic kidney disease (all $p<0.05$). Conversely, young patients were more likely to be male, to smoke, and present a positive family history of cardiovascular disease (all $p<0.05$). Interestingly, the prevalence of prior

Table 1
Baseline patient characteristics.

Feature	Age ≤ 45 years (N = 195)	Age > 45 years (N = 4119)	p value
Age (years)	41.4 \pm 3.5	65.5 \pm 9.7	<0.001
Male gender	176 (90.3%)	3307 (80.3%)	0.001
Family history of coronary artery disease	108 (58.1%)	1373 (35.1%)	<0.001
Hypertension	81 (42.4%)	2718 (67.7%)	<0.001
Dyslipidemia	120 (62.8%)	2317 (57.8%)	0.165
Smoking history	141 (73.8%)	2049 (51.1%)	<0.001
Diabetes mellitus	15 (7.9%)	1081 (26.9%)	<0.001
Chronic kidney disease (serum creatinine > 1.7 mg/dl)	5 (2.7%)	362 (9.2%)	0.002
Prior myocardial infarction	50 (29.2%)	1208 (32.5%)	0.372
Prior percutaneous coronary intervention	37 (21.6%)	991 (26.7%)	0.142
Prior coronary artery bypass grafting	2 (1.2%)	360 (9.7%)	<0.001
Multivessel coronary artery disease	97 (55.4%)	2586 (68.4%)	<0.001
Concomitant unprotected left main disease	9 (4.6%)	318 (7.7%)	0.109
Left ventricular ejection fraction (%)	54.5 \pm 8.0	52.5 \pm 9.4	0.004
Admission diagnosis			<0.001
Stable angina	88 (45.1%)	2141 (52.0%)	
Unstable angina	37 (19.0%)	1001 (24.3%)	
Non-ST-elevation myocardial infarction	22 (11.3%)	453 (11.0%)	
ST-elevation myocardial infarction	48 (24.6%)	524 (12.7%)	
Admission in a low volume center (<800 PCI/year)	59 (30.3%)	1026 (24.9%)	0.093

myocardial infarction and prior percutaneous revascularization did not diverge between the two groups, while older patients had undergone a higher rate of surgical myocardial revascularization ($p < 0.001$).

Clinical presentation was again significantly different: aged patients were mostly admitted for angina, either stable or unstable, and presented more frequently with multivessel coronary artery disease. On the contrary, younger patients had greater frequency of myocardial infarction (STEMI or NSTEMI), and had higher left ventricular ejection fraction (all $p < 0.05$).

Finally, the prevalence of concomitant unprotected left main disease was similar between the groups, as the rate of hospitalization in a low volume PCI center.

3.2. Procedural characteristics

Main lesion and procedural characteristics are outlined in Table 2. The left anterior descending artery was the vessel more frequently involved in both groups, but comparison between bifurcation site in younger and older subject was significantly different (all $p < 0.05$). Particularly, patients ≤ 45 years had higher incidence of left anterior descending/diagonal artery (72.8% vs. 64.0%) and right coronary/posterior descending artery (6.7% vs. 6.3%) involvement. On the contrary, older patients presented more commonly with disease of the left main (8.8% vs. 5.1%), and left circumflex/obtuse marginal artery (21.0% vs. 15.4%). Moreover, while the presence of multiple lesions or restenosis treatment was not significantly different, the rate of true bifurcation lesions was greater in the younger (73.0% vs. 63.3%, $p = 0.009$).

Conversely, few differences were high-lightened in procedural characteristics. As expected, patients ≤ 45 years were more likely to receive drug-eluting stents ($p = 0.008$), but stenting technique was alike between the two groups. Both younger and older patients received mostly stenting of the main branch, while T, V, crushing, culottes or other techniques were used in a minority of patients. Final kissing balloon was performed in about half of the procedures (56.9% of age ≤ 45 years and 51.9% of age > 45 years, $p = 0.168$).

Additional IVUS imaging was effectuated in a minority of patients, and was not significantly different between groups. Vessel diameters

and cumulative stent length was again comparable between younger and older patients.

Finally, both groups had similar duration of dual antiplatelet therapy, and received similar rates of angiographic control during follow up.

3.3. Clinical outcomes

Thirty-day clinical outcomes were comparable in the two groups (Table 3). 2 (1.0%) patients ≤ 45 years suffered a MACE vs. 88 (2.1%) of those > 45 years ($p = 0.439$). Death occurred in 1 younger (0.5%) and in 49 (1.2%) older subjects ($p = 0.388$). Incidence of myocardial infarction, target lesion revascularization and definite stent thrombosis at thirty-day did not significantly differ, although it was slightly more frequent in older patients.

Moreover, the primary end-point was not significant, as the rate of MACE at 24 months did not show any difference between the two groups [25 (12.8%) in age ≤ 45 years vs. 685 (16.6%) in age > 45 years, $p = 0.161$].

Conversely, an increased risk of death was recorded for older patients. The rates of cardiac death (3.3%) and all cause death (5.0%) were higher in aged patients than in younger subjects (0.5% and 1.0% respectively), and the difference proved significant (both $p < 0.05$).

On the other hand, comparable rates were obtained for other clinical outcomes, as incidence of myocardial infarction [6 (3.1%) in age ≤ 45 years vs. 154 (3.7%) in age > 45 years, $p = 0.633$], target lesion revascularization [22 (12.3%) vs. 513 (12.5%), $p = 0.627$] or stent thrombosis [3 (1.5%) vs. 115 (2.8%), $p = 0.294$]. Even at extensive multivariable analysis, younger patients still faced a similar risk of MACE at long-term follow-up, in comparison to older patients (hazard ratio = 0.78 [0.48–1.27], $p = 0.318$).

4. Discussion

In the present study, we compared short and long-term clinical outcomes in younger and older patients treated for coronary bifurcation lesions in the largest dedicated registry data to date, including a total of 4,314 patients. The main findings of this study were: 1) coronary bifurcation lesions represent an interventional challenge, with rates of long-term MACE of 12–16%; 2) early (thirty-day) outcomes did not show significant differences in MACE rates; 3) even though older patients faced an increased risk of death, even long-term rates of MACE were similar between older and younger patients.

Coronary bifurcation lesions account for up to 15%–20% of all current percutaneous revascularizations, and represent challenging subsets,

Table 2
Lesion and procedural characteristics.

Feature	Age	Age	P value
	≤ 45 years (N = 195)	> 45 years (N = 4119)	
Bifurcation site (%)			0.045
Left main	10 (5.1)	363 (8.8%)	
Left anterior descending/diagonal artery	142 (72.8%)	2635 (64.0%)	
Left circumflex/obtuse marginal artery	30 (15.4%)	863 (21.0%)	
Distal right coronary/posterior descending artery/postero-lateral branch	13 (6.7%)	258 (6.3%)	
True bifurcation lesion (%)	127 (73.0%)	2394 (63.3%)	0.009
Multiple lesions on the target vessel (%)	28 (16.0%)	673 (18.2%)	0.460
Restenosis treatment (%)	10 (6.1%)	185 (5.1%)	0.570
Stenting technique (%)			0.061
Main vessel stenting	127 (65.1%)	2685 (65.2%)	
T	16 (8.2%)	525 (12.7%)	
V	33 (16.9%)	614 (14.9%)	
Crushing	8 (4.1%)	115 (2.8%)	
Culottes	10 (5.1%)	100 (2.4%)	
Other	1 (0.5%)	74 (2.0%)	
Drug-eluting stent use (%)	166 (85.1%)	3173 (77.0%)	0.008
Main branch stent diameter (mm)	3.1 \pm 0.4	3.0 \pm 0.4	0.424
Cumulative stent length on main branch (mm)	21.4 \pm 7.8	21.8 \pm 8.2	0.480
Side branch stent diameter (mm)	2.7 \pm 0.4	2.7 \pm 0.4	0.436
Cumulative stent length on side branch (mm)	17.9 \pm 6.9	18.8 \pm 8.6	0.418
Final kissing balloon performed	111 (56.9%)	2137 (51.9%)	0.168
Intravascular ultrasound	9 (4.6%)	217 (5.3%)	0.689
Dual antiplatelet therapy duration (months)	10.3 \pm 8.0	9.8 \pm 8.7	0.504
Angiographic control during follow-up	69 (37.1%)	1359 (33.7%)	0.336

Table 3
Thirty-day and long-term clinical outcomes.

Event	Age	Age	P value
	≤ 45 years (N = 195)	> 45 years (N = 4119)	
Thirty-day outcomes			
Major adverse cardiac events	2 (1.0%)	88 (2.1%)	0.439
Death	1 (0.5%)	49 (1.2%)	0.388
Myocardial infarction	0	38 (0.9%)	0.416
Target lesion revascularization	1 (0.5%)	27 (0.7%)	0.637
Definite stent thrombosis	0	23 (0.6%)	0.623
Long-term outcomes (24.4 \pm 15.1 months)			
Major adverse cardiac events	25 (12.8%)	685 (16.6%)	0.161
Death	2 (1.0%)	205 (5.0%)	0.012
Cardiac death	1 (0.5%)	134 (3.3%)	0.032
Myocardial infarction	6 (3.1%)	154 (3.7%)	0.633
Any target lesion revascularization	22 (11.3%)	513 (12.5%)	0.627
Stent thrombosis			
Definite	3 (1.5%)	56 (1.4%)	0.834
Probable	0	17 (0.4%)	1.0
Possible	0	42 (1.0%)	0.261
Definite, probable or possible	3 (1.5%)	115 (2.8%)	0.294

with lower rates of angiographic and procedural success [14–16]. Given the relative frequency and the overall complexity of coronary bifurcation lesions, many works have addressed this topic, focusing mainly on stenting techniques, and BMS vs. DES use [17–19]. Moreover, many authors have investigated age in large cohorts of patients undergoing PCI, reporting it to be an independent predictor of both in-hospital and long-term mortality [7,20,21]. However, few data are available on outcome in patients receiving treatment for coronary bifurcation lesions stratified by age. Advancing age seems to have detrimental effects on both endothelial function and vascular remodeling, including intimal and medial thickening, and increased wall stiffness [22,23]. Thus, younger age has implicitly been considered a positive prognostic factor. Given this, we aimed to investigate the actual impact of younger age on MACE, both in the short- and long-term, of patients undergoing treatment for complex coronary lesions.

First of all, overall rates of procedural success in our registry were high, with thirty-day MACE reported in 2% of patients, and <1% rate of definite stent thrombosis. Long-term (24.4 ± 15.1 months) MACE occurred in about 16% of the total study population, with rates of death and stent thrombosis respectively of 4.7% and 2.7%. Rates of adverse cardiac events are quite variable across literature, reflecting continuous improvement over time, in stenting techniques and devices [1,15,18,24–27]. Overall, we experienced a relatively low rate of MACE, and our results are in line with previous studies.

Many studies have focused on bifurcation coronary lesions and have reported worst outcome with advancing age [8,28–30]. To assess whether younger age (<45 years) had any impact on outcome, we analyzed data from an Italian multicenter registry of unselected patients undergoing PCI of coronary bifurcations, representing the largest database to date. However, the results of our study are quite unexpected. Young patients face a similar risk of short-term MACE as their older counterpart, with no significant difference in terms of death, myocardial infarction, TLR or stent thrombosis. Moreover, similar results were obtained for long-term outcome, with the exception of death and cardiovascular death, both significantly higher in patients older than 45 years. Baseline characteristics in our population were significantly different between older and younger patients. Unsurprisingly, higher prevalence of hypertension, diabetes, chronic kidney disease, and prior CABG was reported in the older group. Moreover, these patients seemed to suffer from a more severe ischemic heart disease, as they presented higher rates of multivessel disease, lower left ventricular ejection fraction, and left main was more frequently involved.

As reported previously, young patients with ischemic heart disease are more likely to be smokers and to have a positive family history [31–33]. In our registry, while older patients were more likely to present with angina, younger subjects were usually admitted for myocardial infarction. Despite different baseline characteristic, all patients underwent similar treatment; thus, stenting techniques and procedural characteristics differed only in DES or BMS use, since younger patients were more likely to be treated with drug eluting stents. Other characteristics, like stenting technique, stent dimensions, final kissing balloon, use of IVUS, or angiographic control were similar between patients older or younger than 45 years.

As stated above, only death and cardiovascular death in the long-term was significantly different between the two groups. Overall MACE, both at short and long-term follow-up did not diverge. No clear explanation is available for these findings. Age, diabetes, and chronic kidney disease have all been linked to increased risk of death in patients undergoing PCI, thus just the baseline differences could justify increased mortality [6,34,35].

However, these same characteristics have been linked with increased MACE as well, something that clashes with our own results. No obvious explanation can be advocated for this finding. Nevertheless, it could be supposed that in the setting of complex coronary lesions, the most important determinants for major adverse cardiovascular events are related to lesions and procedural characteristic. Accordingly,

positive prognostic factors in complex lesions described in previous registries are low bifurcation angle, use of drug eluting stents, performance of final kissing balloon and complete ostial coverage when using complex two-stents techniques [17,22–25]. In our population, although we miss data regarding bifurcation angle, we recorded similar lesions characteristics and procedural techniques despite age group. Moreover, final kissing balloon was performed with the same frequency in both groups. Thus, it could be postulated that once a complex lesion has developed, the age of the patients is not an independent prognostic factor. The angiographic complexity is such that by itself is enough to determine the outcome. Consequently, age per se was not strong enough to predict better outcomes in patients younger than 45 years. Moreover, since these data are drawn from an all-comers registry, it gives an important insight on outcomes of patients affected by complex coronary lesions in the real world practice.

Therefore, we can conclude that all patients treated with PCI of coronary bifurcation lesions face a non-irrelevant risk of early and late non-fatal adverse events. Younger patients do not fare differently from older patients, and they should not be denied aggressive risk factor modification, medical management and careful follow-up.

4.1. Study limitations

Our study had several limitations, including the non-randomized, observational design. This might have introduced confounding factors. Moreover, the two groups were not homogeneous for baseline characteristic and number, with older patients being over-represented when compared to younger patients. Also, young patients affected by ischemic heart disease may suffer from specific risk factors like coagulation anomalies and thrombophilia, which were not specifically investigated in our database. Finally, the selection of treatment strategies and stent types were at the discretion of the operators, thus having different attitude in younger and older patients, like the significantly different use of DES. Although we performed various risk-adjusted analyses, not all unmeasured variables and confounding factor might have been corrected. However, the observational design and the non-homogeneous populations represent the strength of this registry, that gives an idea of real world practice.

4.2. Conclusion

If it is true that increasing age is a negative prognostic factor, younger age does not necessarily mean risk reduction when dealing with percutaneous treatment of complex coronary lesions. Accordingly, the present study showed that despite their younger age, patients <45 years treated for coronary bifurcation lesions face a risk of adverse short-term and long-term outcome comparable with older patients. Thus, all patients deserve the same aggressive treatment on risk factor modification and close follow-up. Moreover, the finding that short and long-term risk of MACE is similar irrespective of age deserves further investigation.

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All authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology” [36].

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