Clinical Evaluation of Different Revascularization Strategies: Unlabelled Use

Maribel Quezada-Feijoo, Alipio Mangas, Carmen Rodriguez, Eduardo Segura, Carmen Toro-Fernandez, Carlos Gamero, David Gómez-Villarejo, Rocio Toro

ABSTRACT

AIMS: Coronary diseases are the main cause of mortality in the West. Several factors may affect successful percutaneous revascularization, such as the type of stent used or the cardiovascular risk factors associated with the patient. The systolic function of the left ventricle has usually been disregarded in restenosis scores. Our aim is to evaluate restenosis while taking into account the kind of stent used and the systolic function of the left ventricle.

METHODS: A prospective, observational and population study. A total of 209 patients with percutaneous revascularization were recruited between March 2011 and January 2013 and monitored every six months. Their clinical data was collected and transthoracic echocardiograms were performed.

RESULTS: The average age was 67±11 years old, 64.6% were men. Regarding cardiovascular risk factors, 55.6% were diabetics, 84.2% had hypertension and 81.3% were dyslipemic. A combined revascularization strategy was more often used among the general population than in the diabetic subgroup. The diabetic patient subgroup received a larger number of drug-coated stents. The systolic function was present among 84% of the general population compared to 80% of the diabetic patient subgroup. Both the general population as well as the diabetic patient subgroup presented a significant decreased systolic function of the left ventricle when the restenosis rate was greater (p<0.001 respectively). Similarly, we observe that there is a significant connection between the ejection fraction and the emergence of a new symptoms.

CONCLUSION: The non-combined strategy was used more frequently in the diabetic population with the use of a superior drug-eluting stent. Furthermore, systolic function evaluation stratifies the restenosis risk, especially in patients with a depressed ventricular function.

Key words: Stent; Restenosis; Echocardiography; Coronary artery disease

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Abbreviations

ADA: anterior descending artery; ACS: acute coronary syndrome; CVFR: cardiovascular risk factors; CCA: circumflex coronary artery; HBP: high blood pressure; HL: hyperlipemia; LMA: left main artery; LVEF: left ventricular ejection fraction; LV: left ventricle; NIDDM: noninsulin-dependent diabetes mellitus; PCI: percutaneous coronary intervention; RCA: right coronary artery.
INTRODUCTION

In recent years, myocardial revascularization has been the technique of choice for the treatment of coronary diseases. In patients with acute coronary syndrome (ACS), with or without elevation of the ST segment, the myocardial ischemia involves sometimes a vital risk. Biotechnological progress over the last decade has meant that most coronary artery lesions are technically susceptible to treatment by percutaneous coronary intervention (PCI). However, the fact that the implementation is feasible is only one aspect of the therapeutic decision-making process. Until the present time regular clinical practice has meant ad hoc percutaneous intervention, which presents the advantages of being cost-effective and minimizing complications. In order to achieve a more accurate evaluation of which therapeutic approach to follow, a novelty, being introduced to practical clinical guides, is the Heart Team, a multidisciplinary team with the objective of taking controversial therapeutic decisions in a consensual manner[1]. In spite of the predictive burden of coronary heart disease in older patients, this group tends to be systematically excluded from randomized-controlled trials.

At the present time, the revascularization process involves several aspects: age, indications, strategy and the type of stent to implant. Furthermore, there are some other variables to consider, such as clinical factors, cardiovascular risk factors (CVRF) and the ventricular function of the left ventricle (LV). Moreover, drug-coated stents have been associated with a reduction in the restenosis compared to conventional stents; whereas the global and cardiac mortality rates are similar regardless of the stent used[2]. Furthermore, the systolic function, an accessible parameter in daily routines, is a classic indicator of ischemic heart diseases[3]. The quantification of the left ventricular ejection fraction (LVEF) by a transthoracic echocardiogram, adds prognostic information regardless of the information provided by the biochemical markers during the prognosis of more severe episodes during the first 6 months after an ACS[4]. The left ventricular dysfunction and the myocardial ischemia are the principal pathophysiological mechanisms for diagnosing these patients[5]. Nevertheless, it is significant that most scientific works, which have analysed the different prognostic values, have not included the ventricular function in the risk stratification[6].

Our objective is to assess the influence of the ventricular function and the type of percutaneous revascularization carried out on the restenosis risk when considering a population with ACS.

MATERIAL AND METHODS

Study population

This prospective, observational and population study took place over a two year period. A sample size was estimated considering an alpha error of 5%, a statistical power of 95% and an estimated loss ratio of 5%. A total of 209 patients, who had undergone an ACS, were requested to attend the Cardiology Consultation of Villamartin Hospital (Cádiz). They were monitored every 6 months and subjected to a PCI between March 2011 and January 2013. Every patient was informed about the study in detail before signing a consent form.

Definition of the variables

The clinical and demographic data was collected in regard to their case history: age, weight, height, family history, personal information, prior atherosclerotic vascular disease (defined as prior coronary heart disease, cerebral vascular disease or peripheral vascular disease), CVRF: high blood pressure (HBP), non-insulin-dependent diabetes mellitus (NIDDM), hyperlipemia (HL), sedentary lifestyle (Defined as doing less than 30 minutes per day of moderately intense exercise 3 times a week) and having a smoking habit. This smoking habit was classified as either being a smoker or a non-smoker. Drug therapy was also taken into account, as well as information about cardiac catheterization, which included details about affected vessels, the number and type of implanted stent. A combined strategy was also considered in which a conventional stent was placed with a drug-eluting stent. A non-combined strategy was implemented which included the presence of conventional stents or drug-coated stents, thereby avoiding the implementation of both types simultaneously.

During the monitoring period, restenosis episodes were recorded, as well as the need for a new procedure, new symptoms onset or ischemic events (including angina and ischemic infarct).

Every patient underwent a transthoracic echocardiogram in M-mode, two-dimensional, colour flow, continuous wave and pulsed wave Doppler, which was performed with the echocardiography system Philips iE33 The Nederlands with a 5MHz transducer to evaluate the left ventricular function as well as other parameters. The echocardiographic evaluation was performed according to the European Echocardiography Guidelines[7]. The global systolic function of the LV was evaluated in accordance with the Simpson disc method as established[8].

Statistical analysis

The statistical calculations were made with the IBM statistical package Statistical Package for Social Sciences (SPSS), version 19. The normal distribution test was carried out with the Shapiro-Wilk test. The continuous variables followed a normal distribution and were expressed as average ± standard deviation (X±SD). Categorical variables were expressed with frequencies in percentages. To compare the qualitative variables the χ² test was applied. The analysis of the two independent samples was made with the Student’s t-test (normal distribution) or the Mann-Whitney U test.

RESULTS

The characteristics of the clinical population are set forth in table 1. The total prevalence of NIDDM was 55.6% (116 patients). 84.2% were hypertensive, 81.3% were dyslipemic, 11.5% were diagnosed with hyperuricemia and 55% of the total population were smokers. A total of 8.9% had a past history of ischemic heart diseases in their families and 63.6% had experienced a previous ischemic heart episode. In our analysis of NIDDM vs Non-NIDDM population sub-groups, we observed older patients in the diabetic subgroup, with a higher prevalence of females, HBP, HL and those with ischemic heart disease in their family histories, but with a lower prevalence of smokers.

There were no significant differences in the number of affected vessels or in the location of the with the exception of the injuries detected in the left main artery (LMA), which were recurred more among the diabetic population. Furthermore, the diabetic patients received a significantly larger number of drug-coated stents and a non-combined strategy was more frequently used. There were no statistically significant differences regarding the emergence of new ischemic episodes in the monitoring performed on both patient groups.

In performing a more detailed analysis, we note, in regard to the location of the injury, that the use of a combined strategy stands out when there was an effect on the LMA among diabetic or non-diabetic populations. In the middle-distal anterior descending artery (ADA) and in the circumflex coronary artery (CCA), a non-combined strategy was mainly used, compared to a combined strategy which...
was used in the right coronary artery (RCA). In addition, we observe that among patients who received a non-combined revascularization strategy, there is a higher implantation rate of drug-coated stents in all the affected topographic locations. Significant differences emerge in both the proximal and the middle-distal segment of the ADA (Table 2).

The non-diabetic population analysis in table 3 highlights that the majority of the patients with LMA injuries and without a combined strategy had drug-eluting stents implanted. In this regard, a combined strategy was mainly used in the middle-distal ADA, CCA and RCA. In the non-combined strategy subgroup, we observed that the only injuries located in the proximal or middle-distal ADA, had a significant higher use of drug-coated stents. Moreover, in the diabetic groups a non-combined therapy was mainly used for the affection in middle and distal ADA and in the RCA. We have observed a higher implementation of drug-coated stents in all the affected segments, thereby contributing significant value to the proximal ADA.

Most of our aged population exhibited a preserved LVEF, which was higher than 50%, without significant differences between both groups (Figure 1). Considering the study population as a whole, a significant statistical connection is observed between the LVEF and the new symptoms onset (r = -0.32, p < 0.001). This correlation has also been observed in the group of patients with NIDDM. Furthermore, there is a significant connection between LVEF and the emergence of restenosis among the global population (r = -0.27, p < 0.001) and among NIDDM patients (p = 0.006).

**DISCUSSION**

During the two year monitoring period, in our evaluation of an aged-patient population with ACS undergoing PCI, we found that the diabetic population presented a higher prevalence of CVRF, such as HBP, HL and hyperuricemia. It is accepted that individuals over 75 years of age tend to have more diffuse and severe coronary atherosclerosis, a higher burden of calcification, and a higher prevalence of multi-vascular disease, often including LMA involvement. These assumptions highlight the importance of establishing an individualized education plan in order to optimize cardiovascular care and wellness, including discussions about medication adherence, risk reduction strategies and a comprehensive review of all therapeutic options[9]. In this subgroup, there were more females and a higher average age than among the non-diabetic population. Most of those results refer to those in medical literature[10,11].

While the NIDDM is the strongest risk factor associated with the development of ischemic heart disease[12], it is worth highlighting that in all the evolutionary stages of diabetes and for every standard of evaluation, diabetes is always more frequent and serious in

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**Table 1** Basal characteristics and affected vessels in the total population (left). Diabetic versus non diabetic patients (right).

| Variables          | Total population | Non NIDDM (%) | NIDDM (%) | p   |
|--------------------|------------------|---------------|-----------|-----|
| Age (years)        | 67.2±11.1        | 64.5±12       | 68.4±10   | 0.05|
| Male               | 64.6             | 72.8          | 57.3      | 0.02|
| HBP (%)            | 84.2             | 73.9          | 93.9      | 0.001|
| Smoker             | 55               | 73.4          | 42.4      | 0.001|
| Dyslipidemia       | 81.3             | 73.3          | 91.2      | 0.001|
| Hyperuricacidemia  | 11.5             | 4.0           | 17.0      | 0.001|
| Number of affected vessels | 1 | 42.6 | 42.3 | 43.4 | 0.77 |
|                     | 2                | 46.9          | 48.9      | 0.77 |
|                     | 3                | 10.5          | 8.6       | 0.86 |
|                     | LMA (%)          | 7.2           | 13.0      | 2.6  | 0.004|
|                     | Proximal ADA     | 42.2          | 41.3      | 43.2 | 0.88 |
|                     | Middle-distal ADA| 53.8          | 50        | 56.1 | 0.22 |
|                     | CCA              | 38.5          | 61.9      | 62.2 | 0.96 |
|                     | RCA              | 55.3          | 55.4      | 54.3 | 0.88 |
|                     | Non-combined stents | 64.1    | 55.3      | 73.7  | 0.02 |
|                     | Drug-coated stents| 60.3         | 49        | 68    | 0.02 |
|                     | Restenosis       | 24.4          | 30        | 20   | 0.09 |
|                     | New ischemic episodes | 50.2 | 47.7      | 53.9  | 0.4  |
|                     | Angina/AMI       | 41.5          | 52.2      | 46.6 | 0.3  |

Qualitative variables: total (%). Quantitative variables: average (standard deviation). HBP: high blood pressure; LMA: left main artery; ADA: anterior descending artery; CCA: circumflex coronary artery; RCA: right coronary artery; AMI: acute myocardial infarction.

**Table 2** Stent location and use in total population of combined or non-combined stent.

| Variables         | Non-combined therapy, % | NO Conventional Stent, % | COMBINED Drug-coated stent, % | p   | Combined therapy, % | p   |
|-------------------|-------------------------|--------------------------|-----------------------------|-----|----------------------|-----|
| LMA               | 20.6 (55)               | 0 (11)                   | 80 (44)                     | NS  | 5.7 (12)             | <0.001|
| Proximal ADA      | 29.4 (61)               | 29.5 (18)                | 70.4 (43)                   | <0.04 | 24.1 (30)           | <0.05 |
| Middle-distal ADA | 22.2 (46)               | 30.4 (14)                | 69.5 (32)                   | NS  | 16.4 (34)            | <0.05 |
| CCA               | 24.9 (61)               | 49.1 (26)                | 50.8 (31)                   | NS  | 25.6 (53)            | <0.001|
| RCA               |                         |                          |                             |     |                      |     |

LMA: Left main artery; ADA: anterior descending artery; CCA: circumflex coronary artery; RCA: right coronary artery.

**Table 3** Stent location and use of combined or non-combined strategy in NIDDM population. Right: Stent location and use of combined or non-combined strategy in NIDDM population.

| Non diabetic population | Vessel location | Non-combined strategy, % (n) | Conventional stents, % (n) | Drug-coated stents, % (n) | p   | Combined strategy, % (n) | p   |
|-------------------------|----------------|-------------------------------|---------------------------|--------------------------|-----|-------------------------|-----|
| LMA                     | 2.1 (2)        | 3.7 (2)                       | NS                        | 10.8 (10)                | 0.003|
| Proximal ADA            | 21.7 (20)      | 28.3 (15)                    | NS                        | 19.5 (18)                | NS  |
| Middle-distal ADA       | 21.6 (20)      | 26.4 (14)                    | NS                        | 28.2 (26)                | 0.01|
| CCA                     | 17.5 (16)      | 16.9 (9)                     | NS                        | 20.6 (19)                | 0.05|
| RCA                     | 25 (23)        | 26.4 (14)                    | NS                        | 30.4 (28)                | 0.006|
| Diabetic population     | LMA            | 0.02                         |                            |                          |     |                         |     |
| Proximal ADA            | 21.2 (24)      | 36.8 (29)                    | <0.001                    | 11.5 (13)                | NS  |
| Middle-distal ADA       | 34.5 (39)      | 35.5 (27)                    | NS                        | 21.2 (24)                | <0.03 |
| CCA                     | 24.7 (28)      | 27.6 (21)                    | NS                        | 13.2 (15)                | NS  |
| RCA                     | 32.7 (37)      | 31.5 (24)                    | NS                        | 22.1 (25)                | <0.01|
| LMA                     | 2.1 (2)        | 3.7 (2)                      | NS                        | 10.8 (10)                | <0.003|

LMA: left main artery; ADA: anterior descending artery; CCA: circumflex coronary artery; RCA: right coronary artery.
females\(^{13}\). Consistent with our work, in the Odden et al study, diabetes mellitus eliminates the protective effect in women, thereby increasing coronary heart disease risk in this group. Furthermore, it was demonstrated that diabetic females had a lower treatment for modifiable CVRF in proportion to males\(^{14}\).

We have not found any differences between both populations considering the number of affected vessels nor the location of injuries with the exception of those detected in the LMA which were more frequent among the diabetic population.

This could probably be related to the high prevalence of active smokers in this group. It should also be mentioned that regardless of the location of the coronary disease, the NIDDM continues to be an independent risk factor after adjustment is made for the extension of the coronary disease in the angiography and relevant clinical variables\(^{15}\). Roffi et al had concluded from their study that mortality among the diabetic population is double compared to the non-diabetic one, and diabetes is still an independent mortality predictor\(^{16}\). The difference lies with the presence of diabetes, which leads to a higher risk of ischemic heart disease and as a result, early intervention would lead to a greater benefit.

Considering the therapeutic strategies chosen and the kind of stent used among both populations, we observe that diabetic patients are more likely to receive a non-combined therapeutic strategy, as well as a significantly higher number of drug-coated stents. Those results are in line with the Kushner FG et al study, which concluded that patients with high restenosis risk or intra-stent stenosis are candidates for drug-eluting stents\(^{17}\). Nevertheless, indications for myocardic revascularization are not significantly different than for the rest of the population. Our results show the implementation of a higher number of drug-coated stents among the diabetic population and a 56% of unlabelled use indications, which is accompanied by a lower restenosis rate. These results are generally consistent with the recorded results of the authors mentioned above\(^{18-25}\).

Related to the restenosis rate and the emergence of new ischemic episodes, those were higher in the non-diabetic group. This is justified by the type of revascularization therapy employed, considering that in those cases a combined strategy was the main strategy in the diabetic group, who were subject to a non-combined revascularization therapy with a higher number of drug-coated stents.

Insofar as combined therapy, until now there has been no report which considers the implementation of combined stents, drug-coated stents and conventional stents in the same individual. After reviewing the medical literature, we have not found any significant study which analyses a population with these characteristics, so the analysis of the results revealed in our study cannot be subjected to comparative analysis. Nevertheless, it is worth emphasizing its wide implementation among our population which may reflect a general application. In this regard, we consider that a therapeutic strategy is mainly influenced by three variables for the use of stents with unlabelled use indications. The first variable is, undoubtedly, researchers the benefits for a patient, focused on adapting each situation based on risk characteristics and choosing drug-coated stents when there is an estimated clinical probability of restenosis either for diabetes or those with a multi-vessel disease or long-term illnesses or small vessels or any other unfavourable characteristic such as surgery or former percutaneous intervention. A second variable is related to access to cardiac surgery units and the third may be of an economic nature.

When we analysed the appearance of new ischemic episodes related to LVEF, our results coincide with the Bodi et al\(^{26}\) study, where there are higher restenosis rates and patients present a worse ventricular function. Similarly, as Wang et al, we observed a LVEF reduction in our population, which had an independent predictive value for adverse events during the monitoring period when their incidence increases significantly\(^{27}\). Our results are also in line with those from Sardi y cols\(^{28}\) where patients with depressed LVEF -equal or lower than 40%- presented a higher percentage of adverse cardiac episodes and restenosis. In observational studies, the LVEF may be changed, as results demonstrate in the large registers, such as GRACE20 and CRUSADE\(^{29,30}\). Furthermore, it is remarkable that most risk stratification scores produce a secondary value\(^{6,29}\). Gioia G y cols suggest that patients with acute ventricular dysfunction should be deemed a high risk population and precisely for this reason. Implementation of a drug-coated stent is advisable since those stents would decrease the incidence of cardiac adverse effects\(^{32}\).

In our study, we observed a higher restenosis rate and the appearance of new ischemic coronary events in individuals who presented a more reduced LVEF. In this regard, we agree with other authors that the existence of a depressed LVEF in these patients identify the ones with more pervasive coronary disease and therefore, they would benefit the most from potential coronary revascularization.

**LIMITATIONS**

The limitations of this study result from the difficulty of monitoring patients. Since this work is mainly a work of clinical monitoring, we have assessed the patients’ evolution at a cardiology clinic. Observation and monitoring over a longer period and with a bigger population group are required.

**CONCLUSION**

Our work reaches the conclusion that older diabetic patients with combined revascularization therapy present a higher restenosis percentage. In addition, the valuation of the ventricular function provides us with an added value in order to stratify the restenosis risk in patients with a depressed ventricular function.

**ACKNOWLEDGEMENTS**

We wanted to thanks Sara Borjabad Rubio for her translation help.

**CONFLICT OF INTERESTS**

There are no conflicts of interest with regard to the present study.
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Peer reviewer: Christos Voucharas, MD, PhD, Cardiothoracic Department, Blue Cross Hospital, Sourmenon 10, Thessaloniki, 54636 Greece.