In Hospital and 30 Days Results of the Prospective, Observational, Multicenter and Controlled "real world" WALTZ Registry

Resultados hospitalarios y a 30 días del estudio prospectivo, observacional, multicéntrico y controlado del "mundo real": Registro WALTZ

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ABSTRACT

Purpose: To evaluate and describe in-hospital and 30 days clinical outcomes in a real world population treated with a new BMS design and with multiple vessel disease and/or left main coronary artery disease (CAD).
Methods: Since August 2016 to March 2017, 201 consecutive patients undergoing coronary stent implantation in 12 centers in Argentina were included in our registry. Multiple vessel disease and/or unprotected left main disease, acute coronary syndromes , including ST elevation myocardial infarction (MI) and coronary arteries with 70% or more of diameter stenosis, were inclusion criteria. On the other hand, in-stent restenosis, protected left main stenosis or impossibility to receive double antiplatelet therapy for at least one month constitute the exclusion criteria. Primary endpoint was hard clinical end points, defined as any cause of death, MI or cerebrovascular accident. Major adverse cardiac events (MACE) are defined as the incidence of cardiac death, MI, and any ischemic driven lesion revascularization (TLR). Incidence of definitive and possible stent thrombosis (SET) was also analyzed. Baseline and residual Syntax and ERACI score risks were analyzed and compared.
Results: The average age was 61.5 +/- 12 years, 80.1% were men, with a 31.3% of known coronary artery disease and 24.4% with history of MI. The 67.2% of patients had an ACS, of which 31.8% had ST elevation MI. 46.8% of patients had multiple vessel disease and 1.34 vessels per patient were treated in the index procedure. Dual antiplatelet therapy was used in 100% of patients, 52.3% received clopidogrel as charging dose, 11.4% of prasugrel and 36.3% ticagrelor as preferred thyenopiridines. 30 days MACE was 1.5% and cardiac death or any death was 0.5%.Significant differences in baseline (p=0.001) and residual (p<0.01) between Syntax and ERACI score were found. No patients developed stent thrombosis.
Conclusions: In this prospective multicenter observational registry performed in 12 centers of Argentina showed a high 30 days quality PCI performance in a real-world CAD population.

Key words: *stents,bare metal stents, completeness of revascularization, ERACI score, Syntax score.*

RESUMEN

Propósito. Evaluar y describir los resultados hospitalarios y a 30 días en una población de pacientes tratados con angioplastia coronaria (PCI) e implante de un nuevo diseño de stent metálico convencional (BMS), en un amplio espectro de pacientes con infarto agudo de miocardio (MI) , enfermedad de múltiples vasos y tronco de coronaria izquierda en varios centros de nuestro país.
Métodos. Desde agosto de 2016 en marzo de 2017, 201 pacientes consecutivos sometidos a PCI con implante de BMS en 12 centros en Argentina fueron incluidos en nuestro registro. Enfermedad de vasos múltiples o enfermedad de tronco principal de coronaria izquierda desprotegida, síndromes coronarios agudos (ACS), como infarto con elevación ST (MI) y con lesiones en sus arterias coronarias del 70% de estenosis o más fueron criterios de inclusión: reestenosis intrastent, lesiones de tronco no protegido de coronaria izquierda, imposibilidad de recibir doble tratamiento antiplaquetario durante por lo menos de un mes fueron criterios de exclusión. Objetivo primario fueron puntos finales clínicos cardiacos adversos (MACE) definidos como muerte cardíaca, MI o revascularización de la lesión tratada (TLR) evidenciada por isquemia. También se analizó la incidencia de trombosis del stent definitiva o posible (juego). Los scores de riesgo angiográficos basales y posangioplastia (scores de Syntax y ERACI) fueron analizados y comparados.
Resultados. Media de edad fue de 61,5±12 años, 80,1% eran hombres, con 31,3% de enfermedad coronaria conocida y 24,4% con historia de infarto de miocardio 67,2% de los pacientes tenía un síndrome coronario agudo, de los cuales 31,8% eran STE-MI 46.8% de los pacientes tenía enfermedad de múltiples vasos y 1,34 vasos por paciente fueron tratados durante el procedimiento. Doble antiagregación se utilizó en un 100% de los pacientes, 52,3% recibidas clopidogrel dosis de carga, 11,4% de prasugrel y 36,3% ticagrelor como recomendado. A 30 días MACE fue 1,5% y muerte cardíaca o cualquier muerte fue del 0,5%. Diferencias significativas entre los scores de riesgo de Syntax o ERACI basales y post implante del stent fueron observadas (p=0,0001 y p<0,01, respectivamente). Ningún paciente desarrolló trombosis del stent.
Conclusiones: En este registro observacional multicéntrico prospectivo realizado en 12 centros de Argentina se observó un alto suceso clínico y angiográfico hospitalario y a los 30 días en una población de portadores de enfermedad coronaria en el mundo real.

Palabras claves: *stents, stents metalicos, revascularización, score de ERACI, score de Syntax .*

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INTRODUCTION

Nowadays, drug eluting stent (DES) deployment in percutaneous coronary interventions (PCI) are the default strategy with well demonstrated safety and efficacy in a wide range of clinical and /or angiographic circumstances [1, 2]. Notwithstanding its merits, concerns about a higher risk of bleeding or non-complian-

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Figure 1. *Flow chart.*

ce with the mandatory dual antiplatelet therapy suggest considerable contraindications to DES in PCI-patients with specific clinical and socioeconomic conditions[3].On this account, bare metal stents (BMS) have not been abandones. In fact, over 50% of patients receiving a PCI are still treated with BMS in geographic areas where socioeconomic conditions are taken into account. In fact, in Argentina and Brazil, the rate of BMS implantation is higher compared to that of Europe, USA or Canada [4-8].

Additionally, NORSTENT trial, the largest randomized comparison between DES and BMS ever performed, after 6 years of follow up, showed advantages of 2nd DES generation over BMS only in rates of repeat revascularization procedures, without any differences in any cause of death, myocardial infarction or quality of life and these results are in agreement with recent sub-analysis from the BASKET PROVE trial [9-10].

Therefore, despite the greater improvements of DES designs, BMS during PCI has not been disregarded and still has its place, with a 20% penetration in USA [6,11].

Accordingly, the purpose of WALTZ registry, was to perform a multicenter single arm observational study with a novel chromo cobalt stent design in a wide clinical spectrum of patients with coronary artery disease including left main, multiple vessel disease and evolving myocardial infarction.

At our knowledge, there is no prospective observational multicenter and controlled registry with BMS in a real-world cohort of patients previously conducted and published in Argentina [7-8].

Hereby, we are reporting 30 days results of Waltz registry.

MATERIAL AND METHODS

Study Design

Study design was previously reported [12].

Briefly, The Waltz Registry is a prospective, observational, single-arm, multicenter registry that enrolled subjects with a real world atherosclerotic coronary artery lesion in a native coronary artery ≥2.50 mm to ≤4.00 mm in diameter (by visual estimate) in a consecutive all-comers population. The study will be considered complete (in regards to the primary endpoint) after all subjects have completed the 12-month primary endpoint. Between August 2016 to February 2017, 2068 patients were screened in 11 sites in Argentina, 1867 patients didn't meet the inclusion criteria, therefore, 201 patients (9.7%) were finally included in the registry and are the subject of the study **(Figure 1).** Reasons for exclusion are described in Figure 1.

Stent design in the study was a cobalt chromium alloy stent (WALTZ™ Micropart Corp,Shanghai,China) with three different stent designs with enhanced radial strength, flexibility, trackability and pushability. The stent has a strut thickness of 0.0034'' and a crossing profile of 0.037''. Uniform sine wave and "S" links offer excellent balance between supporting strength and flexibility. Its strut with open cells also provides an easy side branch access. The metal covered area is between 11.6 % and 14.3 %.

End Points

Primary end point was the incidence of major adverse cardiac events (MACE) at one year of follow up; however, end points were also measured at 30 days and 6 months of follow up. Secondary end points included the composite of death, MI and CVA; target lesion failure (TLF), stent thrombosis accorded previous definition and to Academic Research Consortium [13-14] and any individual components of MACE. All end points were all analyzed at 30 days, 6 and 12 months of follow up.

Endpoints definitions

MACE is defined as the composite of cardiac death, MI (both ST elevation and Non-ST elevation) and any ischemia-driven revascularization of the target lesion (TLR). Target lesion failure (TLF) is defined as any ischemia driven revascularization of the target lesion, cardiac death (if the event could not be determined with certainty, it will be assumed to be cardiac), MI and TLR. Target vessel revascularization (TVR) refers to an ischemic driven revascularization of the treated coronary artery.

In WALTZ registry, original Syntax Score (SS) was calculated, however, we also used a modification of the original SS, ERACI score, excluding from the analysis all intermediate lesions and severe stenosis in vessels <2.0 mm. This new scoring was in agreement with the

PCI strategy used in the study and was reported in detail elsewhere [15-16].

Furthermore, as part of secondary endpoints in a "post hoc analysis", SS and ERACI risk scores at baseline and after stent deployment were both measured and correlated with late outcome.

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Exclusion Criteria

Subjects are excluded from the study if they have had any of the following:

- Previous treatment at any time with coronary intravascular brachytherapy.
- PCI of a non-target vessel or side branch within 1 day prior to the index procedure.
- PCI of the target vessel or side branch within 12 months prior to the index procedure.
- PCI within 10 mm proximal or distal to the target lesion (by visual estimate) at any time prior to the index procedure.
- In Stent restenosis
- Left ventricular ejection fraction<30%
- Life expectancy less than 1 year
- Contraindication for DAPT therapy

Antiplatelet therapy

Dual Anti-Platelet Therapy (DAPT) was required for all included patients. Aspirin ≥ 300 mg was administrated orally at least 1 hour prior to catheterization and an oral loading dose of thienopyridnes: either clopidogrel (300 to 600 mg), prasugrel (60 mg) or ticagrelor (180 mg), preferably ≥ 6 hours prior to procedure. During PCI unfractionated heparin was recommended as necessary to maintain an activated clotting time as current guidelines suggested. Alternatively, enoxaparin, bivalirudin or others antithrombotic agents could be administrated per standard of care and operator's choice. DAPT will be maintained at least for 1 month and, following the index procedure followed by ASA monotherapy indefinitely. Extended DAPT would be prescribed at the discretion of the investigator, although in patients with acute coronary syndromes (ACS), DAPT was recommended for one year after PCI. Clopidogrel: a maintenance dose of 75 mg per day. Prasugrel: a maintenance dose of 10 mg daily, Ticagrelor: a maintenance dose 90 mg per day.

PCI Strategy

The revascularization strategy was planned prior to the procedure and the aim was to achieve complete revascularization. Percutaneous revascularization was considered functionally complete if no residual severe stenosis (70% or more) remained in any major epicardial vessel and all severe stenosis had been successfully treated with stents.

In addition, completeness of revascularization was defined following residual SS and ERACI score and was arbitrarily calculated using residual risk scores as cut off; residual Syntax score ≤ 5 or residual ERACI score= 0 meant complete anatomic revascularization (CAR). On the contrary, any numbers beyond those limits after PCI were classified as incomplete anatomic revascularization (IAR).

This cut off was selected taking into account that a residual Syntax score ≤5 was linked in several studies with a favorable long term outcome [17-19].

The strategy of staged procedures was not allowed either in target or non-target vessel. According to our previous PCI and stent deployment strategy, mild or intermediate stenosis (50–<70%) was not treated and stent was indicated (by visual estimation) in severe stenosis only; provisional stent strategy was recommended in all bifurcations while strongly discouraged for, severe stenosis in vessels <2.0 mm at it was not to be part of the revascularization strategy[16].

TABLE 1. Baseline characteristics

Male	80.1%
Age	61.5 ± 12.4 years
Age > 80 years	6.5 %
Hypercholesterol	67.1 %
Hypertension	66.7 %
Diabetes mellitus	22.4 %
Current smokers	34.3 %
BMI	27.9 ± 4.2
Acute myocardial infarction previous (AMI)	24.4 %
Previous Revascularization	22.9 %
PCI	21.9 %
CABG	1.00 %
Peripheral vascular disease	4.5 %
Previus Stroke	7.5 %
COPD	6.00 %
Acute Coronary Sindrome	67.2 %
STEMI	31.8 %
Non-STEMI	20.7 %
Unstable Angina	47.4 %
N° of lesions > 70% de estenosis	1.55 ± 0.71
N° of stents implanted	1.49 ± 0.91
Multiple vessels disese	46.8 %
Lesions treated per patients	1.34 ± 0.6
Basal Syntax Score	11.8 ± 6.8
Basal ERACI Score	7.8 ± 5.3
Clopidogrel 600 mg	23.9 %
Clopidogrel 300 mg	28.4 %
Prasugrel 60 mg	11.4 %
Ticagrelor 180 mg	36.3 %

BMI: *body mass index.* ***COPD:*** *chronic obstructive pulmonary disease.* ***PCI:*** *percutaneous coronary intervention.* ***CABG:*** *cardiac artery bypass graft surgery.* ***STEMI:*** *ST elevation myocardial infarction.* ***Non STEMI:*** *non ST myocardial infarction.*

Statistical analysis

The statistical package of SPSS v.17.0.1® (IBM, New York, USA) was used to perform the statistical analysis. Continuous variables were measured using the ANOVA test with Bonferroni correction and categorical variables using chi-square or Fisher's exact test. The continuous variables were expressed as averages

TABLE 2. Differences between angiographic scores.

	SYNTAX score	ERACI score	P value
Basal score	11.8 ± 6.8	7.8 ± 5.3	= 0.0016
Residual score	5.4 ± 5.6	1.3 ± 2.9	< 0.001
Complete revascularization	58%	72%	< 0.01
ERACI score 0			
SYNTAX score ≤ 5			

and standard deviation and the categorical variables were expressed as percentages.

No power calculation was done taking into account that this is an observational study.

Study Organization and Ethical Considerations

An independent clinical events committee will adjudicate all reported events of MACE and other clinical events, including stent thrombosis. An independent data monitoring committee is responsible for overseeing all reported adverse events and evaluating safety data. All the required patient's information needed to fulfill the research was incorporated to the database by each site researchers, trained for that purpose, using a password protected electronic case report form (CRF). The Centro de Estudios en Cardiología Intervencionista (CECI) was responsible for the development of the protocol registry, database, e-CRF and statistics analyses. Per protocol, 25% of patients had a random on site monitoring. The Informed Consent Form (ICF) was presented to the department of justice of protection of people data (Inspección General de Justicia –IGJ-) from Argentina, and the database was approved by this national bureau, following the personal data protection law (Case file Number SO4:0032164/16). The protocol was presented to the National Administration of Food, Drug and Medical Technology (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica -ANMAT-) from Argentina on July 6th of 2016. This is stent was approved for routine PCI by ANMAT on February 19th of 2016 (Case file number 1-47-3110-3045/15-6). The registry follows Good Clinical Practice (GCP) and Helsinki declaration for human research. All patients signed an Informed Consent Form (ICF). During the entire study authorities from ANMAT were aware of study recruitment and adverse events.

On site monitoring from each center will be perform in a random fashion in 25% of patients.

RESULTS

After 5 months of patient recruitment we achieved the goal of 201 patients who met the criteria for inclusion of the study **(Figure 1),** 9.7% of the screened population.

12 centers from different cities of Argentina were selected and included patients in the study.

A list of Hospital and operators are listed in Appendix, the centers are from all over Argentina and included high and medium complexity facilities.

Baseline demographic, clinical and angiographic characteristics of the population are described in **Table 1,** as it shows, there were no restrictions in terms of risk factors either clinically or angiographic. 6.5% of patients were 80 years old or more, including one patient of 100 years old, 22.5% had diabetes, 23% with previous revascularization, COPD in a 6%, previous CVA in a 7.5%, and ACS in the 67.2% of which 32% had STEMI. A presence of multiple vessel disease in 47% of the cohort, 5% of unprotected left main stenosis, and 1.5 stent implanted and 1.34 lesion treated per patient. A loading dose of 600 mg or 300 mg of clopidogrel was taken by 23.9% and 28.4% of patients respectively whereas a loading dose of prasugrel and ticagrelor was taken in 11.4% and 36.3% respectively.

Baseline initial Syntax score was 11.8± but dropped to 7.8 ±when ERACI score was calculated (p=0.0016 for comparison). **Table 2**

TABLE 3. 30 days follow up

	N = 201	%
Death	1/201	0.49
Acute myocardial infarction (AMI)	2/201	0.99
Target lesion revascularization (TLR)	2/201	0.99
Stent thrombosis (ST)	1/201	0.49
Death/AMI	3/201	1.49
MACE	3/201	1.49

MACE: Acute myocardial infarction, stroke, cardiac death.

Hospital and 30 Days Results

There was no procedural related death in the overall cohort of 201 patients. One patient with STEMI, cardiogenic shock and severe ventricular tachycardia died 21 days after PCI in waiting list for cardiac pacemaker and defibrillator (0.5%). Two patients had MI, one STEMI and one non STEMI, one of them had vessel closure for stent thrombosis. The incidence of death plus MI was 1.5% (3/201). Overall MACE at 30 days was 1.5% (3/201). In hospital and 30 days outcome is described in **Table 3.**

After PCI, residual Syntax and ERACI scores were 5.4±5.6 and 1.3±2.9, respectively (p<0.001).

In spite of average of Syntax, score being low, degree of IAR when using such score risk was high, 42% of patients had lesions or vessels without treatment. In contrast, IAR was only 28% (p<0.01 for differences) if we use ERACI risk score, meaning that 72% and 58% achieved complete revascularization according to ERACI and Syntax risk score, respectively (p<0.01).

DISCUSSION

The first analysis of periprocedural and 30 days results of this real-world cohort of patients treated with PCI with a new cobalt chromium alloy BMS, showed a very low incidence of in hospital and 30 days complications. This high procedural (100%) and 30 days survival rate (99.5%) was obtained from 12 PCI centers and operators from different hospitals of Argentina.

The fact that centers included Hospitals with high but also medium complexity facilities, suggest the high standard level of performance reached by PCI operators in our country.
Patients included in this study represent a day by day PCI practice in Argentina with wide range of inclusion criteria: multiple vessel disease (48%), diabetics (22%), acute coronary syndromes including STEMI in the 67%, no age restrictions, a patient over 100 years old, etc, in contrast only limited exclusion criteria was found.
The presence of high numbers of IAR in patients with successful PCI, even in those with single vessel coronary artery disease, was explained by the presence of either severe stenosis in small vessels (<2.0mm) or intermediate stenosis (<70) in large vessel, and operators did not include them in the revascularization strategy and these policy are in agreement to those described by PCI operators using functional flow reserve [20-21]
In agreement, the largest trial comparing PCI vs CABG in left main stenosis, ECXEL trial, the discordances between "on site" and "core laboratory" measurement of SS, was driven by the inclusion of small vessels in the score by "core laboratory" investigators [22] suggesting that PCI investigators "spontaneously" didn't include such lesions into the revascularization strategy.

At this point of the follow up, we still don't know which will be the long-term outcome with such high numbers of IAR or with high residual Syntax risk score in a patient population treated with a BMS implantation.
In a previous study using similar revascularization strategy we did not find major long-term penalties with this sort of PCI strategy [23]. However, those patients had been treated with modern DES design technology that has better efficacy performance than any BMS designs, although in terms of safety events, such as death or MI, large recent randomized data showed that both may be equivalent [9-10.]
In WALTZ registry, either if patients have single or multiple vessel CAD, if target lesion and not target vessel are the main reason of failure at follow up, (meaning coronary restenosis of a BMS), that finding would be in agreement with the revascularization strategy used here
Basal Syntax score and residual Syntax score were reported associated with different risk levels at follow up, however, functional assessment of patients and lesions at the end of PCI procedure appears to be associated with better prognosis predictive value.
Recently, ERACI IV investigators reported that a conservative strategy during DES deployment was associated with a low number of adverse events at follow up. Moreover, they found that residual risk score built following such PCI strategy, had more correlation with the late outcome that the original residual Syntax score has had [19,24].
Accordingly, in the present study, we also found large discrepancies in baseline and residual risk score between both methods of measurements, however, we don't know if the above benefits would also be present in patients treated with BMS design.
Finally, the results of this multicenter, prospective, observational and controlled study (25% of "on site" monitoring and registry was approved by ANMAT) is the first BMS only registry performed and with results reported in Argentina.

Study Limitation

This study has some limitations.
In the first place, it is not randomized and it is only an observational study, although it was prospective, multicenter and "on-site" monitoring was planned in 25% of patients.
Secondly, the sample size is small even though it represents the daily PCI practice in many centers of Argentina where the use of BMS reaches 50% of procedures.
Thirdly, the low incidence of unprotected left main stenosis observed in WALTZ would be associated to the stent design selected in the study.
Finally, we are presenting only 30 days data and, certainly, a one-year outcome would provide us with more information about overall incidence of adverse events and its relationship to PCI strategy.

In Conclusion, this prospective multicenter observational registry performed in 12 centers of Argentina showed a high 30 days quality PCI performance in a real-world CAD population.
One year results should be necessary to asses all end points of the study.

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Appendix

WALTZ REGISTRY STUDY ORGANIZATION

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