World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-34, May 2024
ISSN: 2749-3644

C MIDDLE-DISTANT E AND REMOTE E RESULTS OF USING MAGMARIS BVS - FRAMES IN PATIENTS WITH ACUTE CORONARY EVENTS

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Article history:

Received: February 20th 2024
Accepted: March 24th 2024

Abstract:

Purpose : To study the mid-term and long-term results of using the new generation M agmaris BVS frame in patients with acute coronary artery disease.

Material and methods : 64 patients with acute coronary artery disease were examined, of which 49 were men and 15 were women. The average age of the subjects = 54.3 ± 9.2 (from 33 to 79) years. The acute form of IHD included two nosological units - acute myocardial infarction without a Q wave (group 1 - NSTEMI) - 33 patients and acute myocardial infarction with a Q wave (group 2 - STEMI) - 31 patients. All patients received a biodegradable Magmaris frame . Differences were considered statistically significant at $p < 0.05$.

Results : installation of the Magmaris bioresorbing scaffold in patients with NSTEMI in 9.1% of cases was accompanied by the development of intra-scaffold thrombosis, which was probably due to a decrease in adherence to drug therapy, especially to DAPT therapy ($p>0.05$).

High adherence to drug therapy, and in particular to DAAT tolerance, among patients with a more severe form of the disease (STEMI) ensured good mid-term and long-term results using Magmaris BVS frames .

Conclusion : we hope our work will contribute to the development and improvement of new technologies of modern " bioengineering ". By integrating these developments into various areas of the medical industry, future devices should lead to optimized designs with high levels of safety and effectiveness, which will ensure their wider implementation in clinical practice.

Keywords: bioresorbable frame, coronary heart disease, acute myocardial infarction, coronary angiography

INTRODUCTION .

B V S frames mark the fourth revolution in interventional cardiology. Ultimately, the goal of their development was to overcome the existing limitations of drug -eluting stents . eluting stent or DES stent) by providing temporary support to the vessel wall while allowing the release of an antiproliferative drug to limit the excessive response to potentially allow the vessel to heal and restore its physiological functions.

Magmaris is a Class III medical device in accordance with Directive 93/42/EEC. Magmaris is made of magnesium alloy. It is equipped with permanent round-shaped tantalum radiopaque marks located at both ends of the product. This scaffold itself is radiolucent . Under fluoroscopy, only the stent markers are visible . The stent frame is coated with a polymer coating containing a drug (DP). The nominal drug content in each scaffold is 1.4 µg of sirolimus per 1 mm² of scaffold surface area [1]. Magmaris received the CE mark on June 15, 2016. Conclusions regarding the safety and effectiveness of Magmaris , and therefore compliance with essential requirements, are based on the clinical results of the BIOSOLVE-II, -III and -IV studies [2]. Preliminary study data demonstrated that the early and late complication rates with Magmaris were very low , indicating a very good safety profile, and the target lesion complication rate (TLF) lesion failure) and device thrombosis (TS c – from English. Thrombosis of scaffold) was comparable to various 2nd generation DES stents [3].

On the territory of our Republic, the use of B V S frames is very limited. However, studying the issue of their use

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-34, May 2024
ISSN: 2749-3644

with assessment of immediate, mid-term and long-term results is very relevant.

THE PURPOSE of our work was to study the mid-term and long-term results of using the new generation M agmaris BVS frame in patients with acute coronary artery disease.

MATERIAL AND METHODS .

64 patients with acute forms of coronary artery disease were examined, of which 49 were men and 15 were women. The average age of the subjects = 54.3 ± 9.2 (from 33 to 79) years. The acute form of IHD included two nosological units - acute myocardial infarction without a Q wave (or English: a non-ST-elevation myocardial infarction - NSTEMI) - 33 patients and acute myocardial infarction with a Q wave (eng.: an ST-elevation myocardial infarction – STEMI) – 31 patients.
In the first 24-48 hours of hospitalization of patients in the hospital, control studies were carried out, including: physical examination, ECG in 12 standard leads, EchoCG , clinical and biochemical blood tests (including tests for syphilis, HIV and hepatitis), coagulogram. Also, on the first day of hospitalization, all patients underwent coronary angiography (CAG) with analysis of data on the TIMI scale and assessment of stenoses according to the ACC/AHA classification (2007). Endovascular treatment with percutaneous coronary intervention (PCI) was performed in all 64 patients . All patients were fitted with a biodegradable Magmaris frame
Upon discharge from the hospital, all patients were prescribed basic therapy, including dual antiplatelet therapy (DAPT), beta-blockers (BABs), statins and proton pump inhibitors (PPIs), and, if necessary, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin- II receptor antagonists. (ARA); in the presence of type 2 diabetes - hypoglycemic drugs.
Repeated stages of the study were carried out 6 and 12 months after the CAG procedure with PCI and implantation of the Magmaris frame . The effectiveness of PCI with the installation of a biodegradable Magmaris scaffold was assessed by the number of cases of serious adverse cardiac events (MACE - Major). Adverse Cardiac Events). This collective term (MACE) included:

- Thrombosis frame (eng . thrombosis of scaffold (TSc));
- Revascularization target vessel (eng . target vessel revascularization (TVR;
- Heart attack myocardium , developed V target vessel (English : target vessel myocardial infarction (TV-MI));
- Cardiac death death (CD)).

Depending on the nosological component, the patients were divided into two groups: group 1 – 33 patients with NSTEMI and group 2 – 31 patients with STEMI.
Statistical processing of the obtained data was carried out on a Pentium - IV personal computer using the software package for statistical data processing Statistica 6.0. Descriptive statistics methods included estimation of the arithmetic mean (M) and standard deviation (SD). The reliability of differences between the qualitative indicators of the compared groups was assessed using the χ2 (chi-square) criterion. Comparison between continuous values with a normal distribution was carried out using Student's t-test. To assess the presence of relationships between indicators, a correlation analysis was carried out with the calculation of the Pearson correlation coefficient.
Differences were considered statistically significant at $p < 0.05$. Data are presented as M±SD.

RESULTS .

A comparative analysis of the nature of drug therapy at the time of discharge from the hospital did not reveal significant differences between the compared groups (Table 1); all patients (both with NSTEMI and STEMI) were prescribed DAPT, statins , beta blockers and PPIs. Only nitrates, calcium antagonists (CA), diuretics (including potassium -sparing) in group 2 patients were prescribed more often than in group 1, which was due to the more severe clinical status of these patients. However, the identified differences did not reach the level of significance (all p>0.05).

Table 1.

Drug therapy in the compared groups of patients at the time of discharge from hospital

LP Group	**1 group (NSTEMI) n =33**	**Group 2 (STEMI) n =31**
DAAT	33 (100%)	31 (100%)
Statins	33 (100%)	31 (100%)
BAB	33 (100%)	31 (100%)
IPP	33 (100%)	31 (100%)
Nitrates	4 (12.1%)	7 (22.6%)

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-34, May 2024
ISSN: 2749-3644

ACEI	15 (45.4%)	13 (41.9%)
ARA-2	11 (33.4%)	10 (32.3%)
AK	7 (21.2%)	8 (25.8%)
Diuretics	2 (6.1%)	4 (12.9%)
K^+ - saving	14 (42.4%)	16 (51.6%)
Hypoglycemic	8 (24.2%)	8 (25.8%)
Notes: DAPT - Dual antiplatelet therapy; BAB - Beta-blockers; ACEI - Angiotensin-converting enzyme inhibitors ; ARA-2 - angiotensin-2 receptor antagonists; AK - Calcium antagonists; K^+ - potassium-sparing diuretics; PPI – proton pump inhibitors; all p>0.05.		

An assessment of the dynamics of the drug groups taken among patients with NSTEMI (group 1) found that after six months the patients became less adherent to taking therapy. Namely, taking DAAT and ACEI decreased by 12.1%; statins – by 15.2%; BAB and AK – by 6.1%; IPP – by 18.2%; ARA-2 - by 3.1% and potassium-saving - by half. Only the intake of hypoglycemic drugs did not decrease, which was probably due to the influence of the pathology itself - type 2 diabetes mellitus (Table 2).

An assessment of adherence to therapy 1 year after PCI among individuals in group 1 showed (Table 2) that DAPT intake increased by 9.0% compared to the data at the 6-month stage; but turned out to be lower by 3.1% - compared to the initial indicators. Those. adherence to taking DAPT began to decline in the first six months, which led to the development of TS , the latter, in turn, again contributed to an increase in adherence to therapy, but not in all patients.

A similar picture - a decrease and then an increase in adherence to treatment - was noted with regard to taking drugs from the PPI group: at the 6-month stage, adherence decreased by 12.1%, and at the 12-month stage it increased by 6.1% (compared to with a 6-month stage), but did not reach the values of the initial stage.

At the 12-month stage, a decrease in the intake of the following groups of drugs was observed (Table 2):

- Statins - by 21.2% (compared to the initial stage) and by 6.0% (compared to the 6-month stage, $p < 0.05$);
- BAB – by 15.2% and 9.1%;
- ACE inhibitors – by 15.1% and 3.0%;
- ARA-2 – by 3.1% and 3.1%;
- AK – by 6.1% and 6.1%;
- K-savers – by 30.3% and 9.1%, respectively.

Due to the improvement in clinical status, taking nitrates and diuretics at the 6-month stage. was no longer required, however, hypoglycemic drugs remain for lifelong use (since diabetes is still an incurable disease), which was the case in our patients (Table 2).

Table 2.
Dynamics of drug therapy among patients with NSTEMI

LP Group	**Exodus n =33**	**6 months n =33**	**p1**	**12 months n =33**	**p2**
			χ2		**χ2**
DAAT	33 (100%)	29 (87.9%)	0.122	32 (96.9%)	1,000
			2,395		0.000
Statins	33 (100%)	28 (84.8%)	0.063*	26 (78.8%)	**0.016**
			3,462		**5.753**
BAB	33 (100%)	31 (93.9%)	0.473	28 (84.8%)	0.063*
			0.516		3,462
IPP	33 (100%)	27 (81.8%)	0.032	29 (87.9%)	0.122
			4,583		2,395

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Available Online at: https://www.scholarexpress.net
Volume-34, May 2024
ISSN: 2749-3644

Nitrates	4 (12.1%)	-	0.122 2,395	-	0.122 2,395
ACEI	15 (45.4%)	11 (33.3%)	0.450 0.571	10 (30.3%)	0.310 1,030
ARA-2	11 (33.4%)	10 (30.3%)	1,000 0.000	10 (30.3%)	1,000 0.000
AK	7 (21.2%)	5 (15.1%)	0.750 0.102	5 (15.1%)	0.750 0.102
Diuretics	2 (6.1%)	-	0.473 0.516	-	0.473 0.516
K^+ - saving	14 (42.4%)	7 (21.2%)	0.113 2,514	4 (12.1%)	**0.013** **6,188**
Hypoglycemic	8 (24.2%)	8 (24.2%)	0.774 0.083	8 (24.2%)	0.774 0.083
*Notes: DAPT - Dual antiplatelet therapy; BAB - Beta-blockers; ACEI - Angiotensin-converting enzyme inhibitors ; ARA-2 - angiotensin-2 receptor antagonists; AK - Calcium antagonists; K^+ - potassium-sparing diuretics; PPI – proton pump inhibitors; * - tendency towards reliability; p1 - reliability of differences between the outcome data and the 6-month stage; p2 – significance of differences between the outcome data and the 12-month stage*					

Among patients in group 2 (i.e., with a diagnosis of STEMI), the assessment of adherence to drug therapy at stages turned out to be more positive, compared with similar indicators for patients in group 1 (i.e., with a diagnosis of NSTEMI) (Table 3).

Table 3.
Dynamics of drug therapy use among patients with STEMI

LP Group	**Exodus n =31**	**6 months n =31**	**12 months n =30**
DAAT	31 (100%)	31 (100%)	30 (100%)
Statins	31 (100%)	30 (96.8%)	30 (100%)
BAB	31 (100%)	30 (96.8%)	28 (93.3%)
IPP	31 (100%)	29 (93.5%)	28 (93.3%)
Nitrates	7 (22.6%)	-	-
ACEI	13 (41.9%)	12 (38.7%)	10 (33.3%)
ARA-2	10 (32.3%)	10 (32.3%)	9 (30.0%)
AK	8 (25.8%)	6 (19.3%)	5 (16.7%)
Diuretics	4 (12.9%)	3 (9.7%)	1 (3.3%)
K^+ - saving	16 (51.6%)	15 (48.4%)	10 (33.3%)
Hypoglycemic	8 (25.8%)	8 (25.8%)	8 (26.7%)

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Volume-34, May 2024
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Notes: DAPT - Dual antiplatelet therapy; BAB - Beta-blockers; ACEI - Angiotensin-converting enzyme inhibitors ; ARA-2 - angiotensin-2 receptor antagonists; AK - Calcium antagonists; K^+ - potassium-sparing diuretics; PPI – proton pump inhibitors; all p>0.05

In particular, until the end of this study, all patients took DAPT, and the intake of statins , beta blockers and PPIs during the stages was over 90% (Table 3).

The final 12-month stage of the study included 30 patients from group 2, 1 patient did not appear for the 12-month stage of the examination (went abroad) and was excluded from this sample.

Table 3 shows in detail the dynamics of the drug groups taken among patients with STEMI . As presented in Table 3, among patients in group 2, all (100%) patients took DAPT until the end of the study.

A decrease in adherence was observed in the following drug groups (Table 3):

- statins – at the 6-month stage. – by 3.2% compared to baseline, but at the 12-month stage the level of adherence was again 100%;
- BAB – by 3.2% and 6.7%, respectively, 6 and 12 months after PCI;
- IPP – by 6.5% and 6.5%;
- ACE inhibitors – by 3.2% and 8.6%;
- ARA-2 – by 0% and 2.3%;
- AK – by 6.5% and 9.1%;
- Diuretics – by 3.2% and 9.6%;
- K-savers – by 3.2% and 18.3%, respectively.

As for hypoglycemic drugs, as in group 1, adherence did not change and remained intact (Table 3).

Decreased adherence to drug therapy at 6 months. led to the fact that among patients in group 1, the total MACE rate was 9.1% and was represented by three cases of intraframework thrombosis (TSc). In particular, 2 patients stopped taking DAPT on their own and after 3 months. they developed device thrombosis and another 1 patient also stopped taking DAPT after 4 months. after PCI, TS also developed (Table 4).

Perhaps the less severe form of the disease (NSTEMI), as well as awareness of the subsequent resorption of the device, contributed to the early spontaneous refusal of patients to take medications, in particular taking DAPT, which ultimately provoked 9.1% of cases of MACE in patients of group 1 or 4. 7% of MACE cases, in general, in the study sample with installed biodegradable scaffolds of the new generation Magmaris .

A similar assessment of the level of adherence in relation to the development of MACE showed that it was probably the high continued adherence to therapy, and in particular to DAPT therapy, among patients with STEMI that contributed to the fact that their total MACE score was "0" at all subsequent stages (Table 4), which, in turn, can be regarded as good effectiveness of the Magmaris frame in terms of use in patients with acute coronary artery disease, in particular with STEMI .

Table 4.

Dynamics of MACE in the compared groups of patients

MACE		**1 group (NSTEMI)**	**Group 2 (STEMI)**
Stages:		**n =33**	**n =31**
6 months:	TS with	3 (9.1%)	0
	TVR	0	0
	TV - MI	0	0
	CD	0	0
12 months:	T.S.	3 (9.1%)	0
	TVR	0	0
	TV - MI	0	0
	CD	0	0
TOTAL (n=64)		3 (4.7%)	
TS – stent thrombosis of stent); TVR – target vessel revascularization (target vessel revascularization); TV - MI – heart attack myocardium target vessel (target vessel myocardial infarction); CD – cardiac death death).			

When conducting a correlation analysis between the nosological component and the total MACE indicator, an inverse relationship was established, which, however, did not reach the level of reliability (Fig. 1). Those. A less severe form of

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-34, May 2024
ISSN: 2749-3644

the disease, in particular NSTEMI, was accompanied by a higher incidence of adverse cardiac events (MACE), namely TS c.

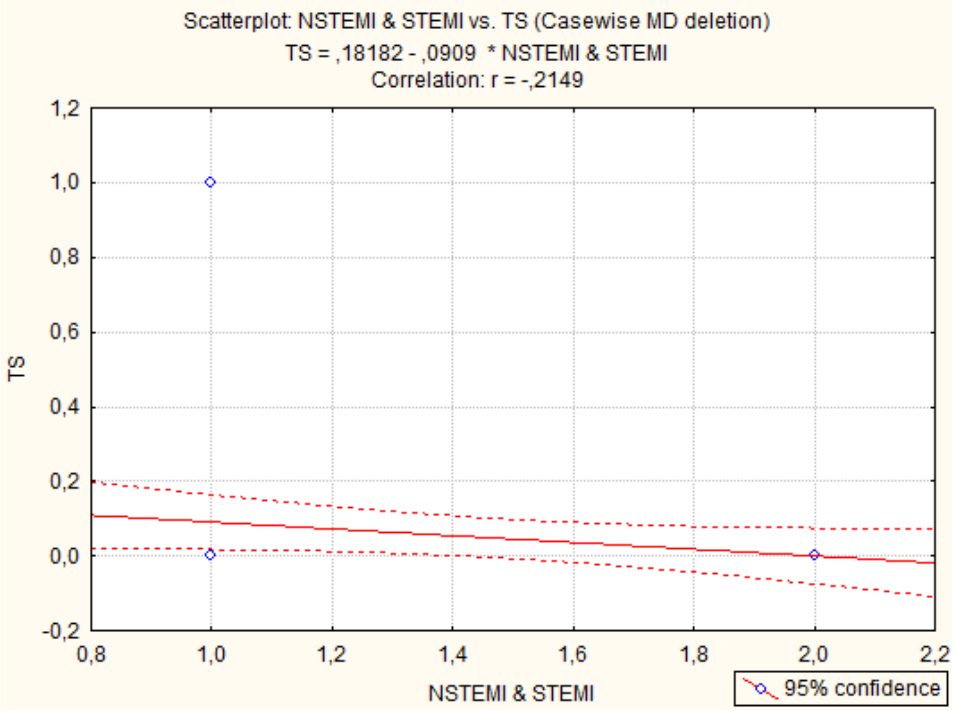

Figure 4.1 . **Graph of the correlation between the nosological component and cases of device thrombosis (TS c).** p= 0.088 ; r= -0.214 and t= - 1.732

Notes: On the X axis – under the number "1" - patients with a diagnosis of NSTEMI and under the number "2" - patients with a diagnosis of STEMI ; along the axis Y – cases of device thrombosis .

DISCUSSION .

The use of BVS scaffolds in patients with coronary artery disease is currently limited in daily clinical practice due to safety concerns and the 2018 European Society of Cardiology guidelines on myocardial revascularization , which do not recommend the use of BVS scaffolds for clinical use outside of clinical trials [4]. Despite this, more and more positive data are emerging on the effectiveness and safety of the use of BVS frames in patients with stable coronary artery disease and in selected patients with ACS.

Today, the concept of BVS frames continues to be attractive. One of the encouraging representatives of this type of device is the scaffold Magmaris is a new frame made of absorbable magnesium alloy, completely covered with the biodegradable polymer poly-L- lactide (PLLA) " BIOlute ". Initial data showed an acceptable safety profile for this device, especially in terms of intraframe thrombosis.

In the PRODIGY study, 2013 patients were randomized to receive DAPT (aspirin + clopidogrel) for 6 and 24 months with a primary composite outcome of all-cause mortality, MI, stroke, or stroke.

Analysis of pure MACEs demonstrated an increase in their incidence with prolongation of DAPT in the group of people with stable CAD (13.3 vs. 5.6%; RR 2.5; 95% CI [1.35–4.69]; p=0.004), but not in patients with ACS (16.1 vs. 14.1%). ; OR 1.15; 95% CI [0.88–1.50]; p=0.29) [5].

Several other studies since 2014 have confirmed the superiority of short-course DAPT, the largest of which was the ISAR - SAFE trial , a double-blind, randomized trial of 4005 patients, of whom 60% had stable CAD and 40% had ACS. The study compared 6 months of DAPT (aspirin + clopidogrel) with 12 months of DAPT and found that there was no difference in the incidence of the primary composite endpoint in either patients with ACS or patients with stable CAD [6].

In Michael's study J. Lipinski et al . [7], it was found that in 5 of 14 cases, BVS frame thrombosis occurred after cessation of DAPT, and therefore the authors recommend avoiding the use of BVS frames in people

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Available Online at: https://www.scholarexpress.net
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ISSN: 2749-3644

requiring PCI if there are concerns about non-compliance with the treatment regimen.
Our work suggests that the Magmaris BVS frame can be used in patients with acute coronary artery disease, but strict monitoring of DAPT intake is required.

CONCLUSION .

Installation of the Magmaris bioresorbing frame in patients with NSTEMI in 9.1% of cases was accompanied by the development of intraframe thrombosis, which was probably due to a decrease in adherence to drug therapy, especially to DAPT therapy (p>0.05)
High adherence to drug therapy, and in particular to DAAT tolerance, among patients with a more severe form of the disease (STEMI) ensured good mid-term and long-term results using Magmaris BVS frames .
We hope our work will contribute to the development and improvement of new technologies of modern " bioengineering ". By integrating these developments into various areas of the medical industry, future devices should lead to optimized designs with a high level of safety and effectiveness, which will ensure their wider implementation in clinical practice

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