UNIVERSITY OF PIRAEUS

DEPARTMENT OF BUSINESS ADMINISTRATION

Executive-MBA Program

Executive-MBA Thesis

Cost Effectiveness and Social Benefit of Resorbable Magnesium Scaffolds in Coronary Artery Disease patient subgroups

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ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΕΙΡΑΙΩΣ
ΣΧΟΛΗ ΟΙΚΟΝΟΜΙΚΩΝ ΕΠΙΧΕΙΡΗΜΑΤΙΚΩΝ ΚΑΙ ΔΙΕΘΝΩΝ ΣΠΟΥΔΩΝ
ΤΜΗΜΑ ΟΡΓΑΝΩΣΗΣ ΚΑΙ ΔΙΟΙΚΗΣΗΣ ΕΠΙΧΕΙΡΗΣΕΩΝ
ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΣΤΗ ΔΙΟΙΚΗΣΗ ΕΠΙΧΕΙΡΗΣΕΩΝ ΓΙΑ ΣΤΕΛΕΧΗ

ΒΕΒΑΙΩΣΗ ΕΚΠΟΝΗΣΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

(περιλαμβάνεται ως ξεχωριστή (δεύτερη) σελίδα στο σώμα της διπλωματικής εργασίας)

«Δηλώνω υπεύθυνα ότι η διπλωματική εργασία για τη λήψη του μεταπτυχιακού τίτλου σπουδών, του Πανεπιστημίου Πειραιώς, στη Διοίκηση Επιχειρήσεων για Στελέχη : E-MBA» με τίτλο Cost Effectivenes and Social Benefit of Resorbable Magnesium Scaffolds in Coronary Artery Disease patient subgroups έχει συγγραφεί από εμένα αποκλειστικά και στο σύνολό της. Δεν έχει υποβληθεί ούτε έχει εγκριθεί στο πλαίσιο κάποιου άλλου μεταπτυχιακού προγράμματος ή προπτυχιακού τίτλου σπουδών, στην Ελλάδα ή στο εξωτερικό, ούτε είναι εργασία ή τμήμα εργασίας ακαδημαϊκού ή επαγγελματικού χαρακτήρα.

Δηλώνω επίσης υπεύθυνα ότι οι πηγές στις οποίες ανέτρεξα για την εκπόνηση της συγκεκριμένης εργασίας, αναφέρονται στο σύνολό τους, κάνοντας πλήρη αναφορά στους συγγραφείς, τον εκδοτικό οίκο ή το περιοδικό, συμπεριλαμβανομένων και των πηγών που ενδεχομένως χρησιμοποιήθηκαν από το διαδίκτυο. Παράβαση της ανωτέρω ακαδημαϊκής μου ευθύνης αποτελεί ουσιώδη λόγο για την ανάκληση του πτυχίου μου».

Υπογραφή Μεταπτυχιακού Φοιτητή/ τριας........................

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Dedicated to

The current analysis is dedicated to my parents Nikolaos and Margarita and my son Thomas-Markellos.

Table of Contents

Abbreviations and acronyms

ACS = Acute Coronary Syndrome

AF = Atrial Fibrillation

AIDA = Amsterdam Investigator-Initiated Absorb Strategy All-Comers

AMI = Acute Myocardial Infarction

ARC = Academic Research Consortium

BMS = Bare Metal Stent

BRS = BioResorbable Scafflds

BVS = Bioresorbable Vascular Scaffolds

CABG = Coronary Artery Bypass Grafting

CAD = Coronary Artery Disease

CKD = Chronic Kidney Disease

CTO = Chronic Total Occlusion

CVD = Cardio Vascular Disease

DALYs = Disability Adjusted Life Yeas

DAPT = Dual Antiplatelet Therapy

DCB = Drug Coated Balloon

DES = Drug Eluting Stent

EACTS = European Association for Cardio-Thoracic Surgery

EAPCI = European Association for Percutaneous

EF = Ejection Fraction

ESC = European Society of Cardiology

EuroSCORE = European System for Cardiac Operative Risk Evaluation

FUP = Follow-UP

GBD = Global Burden of Diseases, injuries and risk factors

HF = Heart Failure

IHD = Ischemic Heart Disease

IHME = Institute for Health Metrics and Evaluation

ISR = In-Stent Restenosis

IVUS = IntraVascular Ultrasound Imaging

MACCE = Major Adverse Cardiac and Cerebrovascular Events

MACE = Major Adverse Cardiac Events

NSTE-ACS = Non-ST-segment Elevation Acute Coronary Syndrome

NSTEMI = Non-ST-segment Elevation Myocardial Infarction

OCT = Optical Coherence Tomography

OOP = Out-Of-Pocket

PPYLL = Potentially Productive Years of Life Lost

SCAD = Stable Coronary Artery Disease

STEMI = ST-segment Elevation Myocardial Infarction

SYNTAX = Synergy between Percutaneous Coronary

TIMI = Thrombolysis in Myocardial Infarction

YLD = Years Lost due to Disability

YLL = Years of Life Lost

Summary

Keywords: economic crisis, cost effectiveness, social benefit, macro- and micro-economy, payment terms

Economic crisis in Greece has caused a trauma to quality of life of the population. Due to austerity program, healthcare expenditure has been decreased and innovative technologies have limited access to the market. Innovative products are supposed to be costly. But are they? How can we claim that a technology is costly and in which way is it? If the criteria is just the product price, then of course, innovation is expensive. Still, if we compare the long-term benefits of innovative technologies to the initial cost, then the result may be the opposite.

The aim of the current analysis is dual dimensional. Concerning the one dimension, we will explore if RMS might be cost effective and / or have social benefit in coronary artery disease subgroups of patients. Since we are not physicians and it is only them to identify the subgroups, we will have our estimations based on the Scientific Committee of the National Tender regarding the share of the scaffolds and on the fact that RMS have approximately zero scaffold thrombosis. We will estimate the indirect cost and its consequences on macro- and micro-economy based on PPYLL and DALYs. We will also estimate the direct cost by comparing the initial extra cost due to RMS use and the cost due to re-hospitalization and revascularization because of stent thrombosis and extension of dual antiplatelet therapy. With regard to the second dimension, we will explore coexistence of factors that may influence the technology price. By clarifying these factors and the way they affect to the product price and continuously to the budget, we will suggest alternative, non-costly approaches to the technology.

In order to conclude, Resorbable Magnesium Scaffolds technology seem to be cost effective and socially beneficial in patients with high risk of potential stent thrombosis, young patients and babies or children. Payment terms seem to be the key factor to achieve innovation embody to the market without increase of healthcare expenditure. Additionally, increase of budget leads to price decrease followed by increase of volume and number of patients who might have the benefits of the technology.

Introduction

As R. A. Byrne, et al, 2015, report, on 16th of September 1977, Andreas Grüntzig performed the first Percutaneous Coronary Intervention (PCI), using a balloon catheter fashioned on his kitchen table. High level of restenosis and vessel recoil, led to Bare Metal Stents (BMS) development. Due to Stent Thrombosis (ST) and In-Stent Restenosis (ISR) of BMS, first generation of Drug Eluting Stents (DES) were developed. Although, 1st generation DES managed to eliminate ISR, Stent Thrombosis rates were increased due to polymer which caused incomplete endothelialization of the struts. Second generation DES seem to be quite efficient as it concerns ST rates, especially in Stable Coronary Artery Disease (SCAD) patients. However, several issues are still not solved. Strut fractures, Very Late Stent Thrombosis (VLST), neoatherosclerosis, vasomotion dysfunction, allergic reactions, are a part of the post-PCI issues to be considered. Innovative technologies, such as Resorbable Magnesium Scaffolds (RMS), have appeared demonstrating encouraging long-term clinical results on respect to vasomotion, very late thrombosis and neoatherosclerosis, while struts fractures and allergic reactions are eliminated since the device is resorbed.[1]

Coronary artery disease may be considered as quite costly. According to American Heart Association (AHA), 2017, publication, and on regards to cost projection due to Cardio Vascular Disease (CVD), the burden of disease in 2016 was $555 billion and as it projected it will rise to $1.1 trillion by 2035. As it concerns Coronary Artery Disease (CAD), the estimated indirect cost due to loss of productivity will be increased by 55%, from $99 billion to $151 billion in 2035, while medical cost will face a rise from $89 billion to $215 billion respectively.[2]

Since 2010, due to economic crisis in Greece, a health expenditure reduction has taken place. Innovative technologies presence is quite limited as the medical centers can not afford the extra burden. However, several publications, claim that well scheduled use of innovative products or procedures may be cost effective. For example, as J. Kanakakis, et. al.,2012, claim on a Stent For Life (SFL) report, based on recent studies, primary-PCI (p-PCI) treatment for patients with acute ST-segment Elevation Myocardial Infarction (STEMI), is socio-economically cost effective, regardless the required cost.[3]

The ancient Greek god “kairos” was the personification of opportunity. As he had only one lock of hair on the front and wings on his back, the opportunity should be caught from the hair as “kairos” was passing by in front of you, otherwise, “kairos” would fly away and the opportunity would have been lost…

Greek crisis has revealed quite a few weaknesses and it is our task to move forward. Still, in order to do the right things, we should do it right.

The aim of this analysis is to indentify if Magnesium Scaffold implantation might be Cost Effective and Socially Beneficial in subgroups of Coronary Artery Disease patients. As the physicians are the only who have the knowledge and experience to identify the issues they have to face due to stent implantation and the subgroups of patients that may have benefits because of RMS use , based on their presentations, it is as following:

Issues to be solved: a) chronic mechanical stress, b) neoatherosclerosis, c) very late stent thrombosis, d) difficulties in surgical grafting, e) stents fractures, f) stent malapposition, g) vasomotion dysfunction.

Concerning RMS candidates, physicians claim that it might be: a) young patients, b) pediatric cases, c) STEMI patients, d) bifurcation cases, e) diffused lesions f) patients with high complex lesions and g) DAPT non responders.

Regarding the current market situation, as the National Tender (NT), 2014, has requested and based the real market status, approximately 80% of the stents are second generation Drug Eluting Stents. According to the NT and the scientific committee, due to low budget and lack of data of that period, scaffolds category should concern approximately 4.14% of the total stents quantity.[4] However, the market implanted RMS quantity is far lower because of low hospital budget and absence of Diagnosis Related Group (DRG) and Price Observatory Category. Based to the pre-mentioned, we will report several topics of the CAD, 2nd generation DES and RMS performance as it concerns the clinical outcomes and the market penetration.

Based on the approximately zero Scaffold Thrombosis (ScT) that RMS have demonstrated, we intent to explore, if the high initial burden, due to innovative technology use, is lower than the final macro- and micro-economy cost due to death, disability and loss of productivity by estimations of Potentially Productive Years of Life Lost (PPYLL) and Disability-Adjusted Life Years (DALYs). Additionally, we will compare the extra burden of RMS implantation and the cost of potential re-hospitalization in CAD patient subgroups. Furthermore, we will identify the number of RMS per patient that might be implanted in order the technology be cost effective and compare the duration of prolonged Dual Antiplatelet Therapy (DAPT) with the RMS implantation.

In addition, we will create a graph regarding the number of patients that might be treated with RMS, depended on budget, product price and payment terms. The aim is to explore alternative ways of increasing the number of patients who might have the benefits of the technology, without increase of budget.

As the average age of population facing Ischemic Heart Disease (IHD) is decreased, the Greek workforce is more affected and the country macro- and micro-economy burden due to disease becomes heavier. The cost effectiveness and social benefits analysis expectations are to explore and identify opportunities that might allow innovative technology products offer their benefits to higher part of population without necessity of increase of health expenditure.

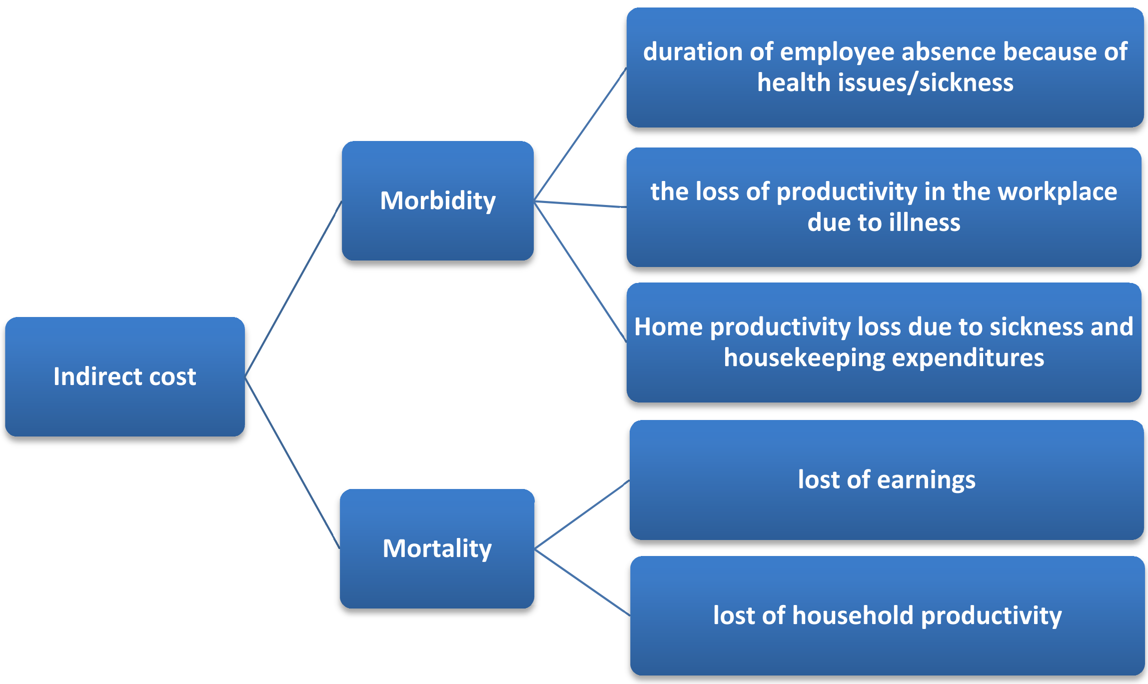
Chapter 1

Coronary Artery Disease: A multidirectional threat

1.1 Indirect Cost and the Affects in Macro and Micro-economy

1.1.1 Introduction

The indirect cost is quite difficult to be measured. While as direct cost, ambulances, hospital and medical care, outpatient care and health services are included and could more easily be calculated, as indirect cost it is the lost of productivity, in both workplace and home, that it concerns. Indirect cost is divided to indirect cost due to morbidity and indirect cost due to mortality, as following:[2]



According to S.Leeder, et. al., 2014, 2nd edition of “A Race Against Time”, indirect cost is associated to two measures, Potentially Productive Years of Life Lost (PPYLL) and Disability-Adjusted Life Years (DALYs). DALYs are calculated as the sum of Years Lost due to Disability (YLD) and Years of Life Lost (YLL).[5]

In an effort to estimate the relevance between Cardio Vascular Disease (CVD) and PPYLL, a group of five Low-Middle Income Countries (one low and four middle ones) and a group of two industrialized countries were studied. On regards on YLD per 100,000 of population, a subgroup analysis took place concerning groups of work force 35-39, 45-49 and 55-59 years old, based on Global Burden Disease Study, 2012.[5]

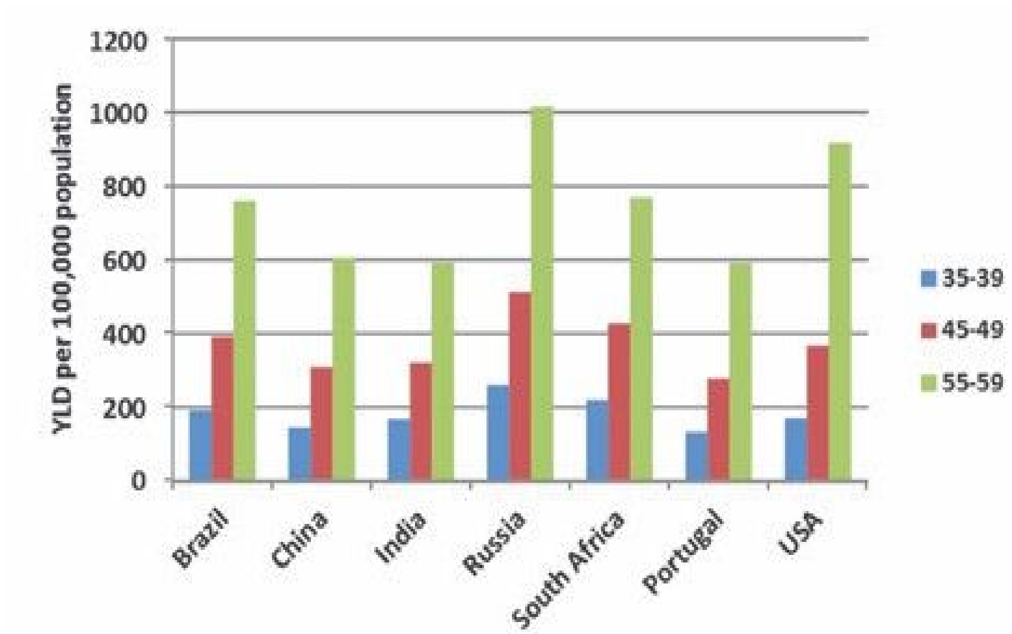


Figure1.1 Years lost due to disability (YLD) estimates – YLD per 100,000 population due to cardiovascular and circulatory diseases – among three working age groups, 35–39, 45–49 and 55–59 years. Source: Global Burden of Disease Study 2012. http://viz.healthmetricsandevaluation.org/gbd-compare

Additionally, PPYLL between the countries of the groups was estimated concerning 2008 and the potentially rates in 2050 in population aged 35-64 years.[5]

Table 1.1: Out-of-pocket (OOP) expenditures for CVD as a proportion of overall OOP health expenditures, 2007.[5]

	OOP for CVD
USA	23%
Portugal	77%
South Africa	30%

	2008 Total	2050 Total
South Africa	117,963	199,694
Brazil	466,987	741,065
China	1,915,517	2,247,802
India	5,724,975	11,920,506
Russian Federation	1,683,343	1,362,436
Sub Total	9,908,785	16,471,503

	2008 Total	2050 Total
USA	784,173	909,251
Portugal	12,909	10,052
Sub Total	796,382	919,303

Table 1.2: Potentially productive years of life lost (PPYLL) due to cardiovascular disease (CVD) among the populations aged 35–64 years for the five study and two comparator countries for 2008 and 2050, assuming current CVD mortality trends continue.The same analysis estimated the Out – Of - Pocket (OOP) health spending, which is the burden CVD individuals pay in private sector or any other health relevant. Data from the study show that in 2007, OOP varied from 30% of overall health expenditures, in South Africa, to 92% of overall health expenditures in China.[5]

The cost of CVD is quite high and its component Coronary Heart Disease (CHD), (or Coronary Artery Disease (CAD) or Ischemic Heart Disease (IHD)), requires the most of the CVD expenditure, due to increased cost of procedure and products.
An analysis of direct and indirect cost in EU, in 2010, showed that the estimated overall indirect cost was €16.6 billion, while the direct was even higher, €23.98 billion.[5]

Table 1.3: EU Direct and Indirect cost

		CHD				STROKE		
	DIRECT	INDIRECT			DIRECT	INDIRECT		
		Due to Morbidity	Due to Mortality	Informa Care		Due to Morbidity	Due to Mortality	Informa Care
EU (Billion Euros)*	23.98	12.3	4.3	9.1	18.5	4.78	3.68	11.1
EU (Billion 2006 Int Dollars)	37.17	19.06	7.13	14.1	26.7	7.41	5.7	17.2
USA (Billion 2010 Int Dollars)**	96	11.3	69.8	--	48.2	7.5	18	--

Table 1.3. Direct and indirect costs due to cardiovascular disease in the European Union (EU) and the United States of America (USA). * British Heart Foundation (19). ** American Heart Association (16).

To summarize, CVD and its component CHD are major causes of PPYLL and DALYs. The loss of productivity due to morbidity and mortality has potential macroeconomic consequences. An investment to higher quality of health treatment using innovative products that elongate life duration and improves quality of life, drives the population to enhanced productivity and strengthens the countries' macro-economy.

1.1.2 EU-Greece-Portugal

Concerning the population, Greece and Portugal share approximately equal part of the European inhabitants by 2.1% and 2.0% respectively, with the Greeks reaching 10,757,300 of 511,805,100 of the Europeans.[6]

In May 2018, a selection of key indicators were provided by the European Parliament and concern Member States that are or have been subject to a Macroeconomic Adjustment Program. A comparison between European Union (EU), Greece and Portugal shows that in 2016 the EU GDP per capita – purchasing power parity was 31,000€ while in Greece and Portugal was 19,700€ and 22,600€ respectively.[7]

A closer look at Greece and Portugal, shows that though the two countries share almost equal share of population in the EU, and though the GDP per capita – PPP rates do not differ each other that much, several indicators may reveal the social-economy picture. General Government Gross Dept, with the Greek been quite higher, is not the only issue the country has to deal with. The Greek labor force face increased unemployment to both the overall and young ones'. While in Portugal the overall unemployment was 11.2% and the young unemployment 28.2% in 2016, in Greece the overall was 23.6% and the young one 47.3%.

Additionally and as a result of the above, the Greek households seem not be able to perform private loans to the bank sector, having 46.7% non-performing in total loans, while in Portugal the non- performing ones are 19.5%.

Moreover, due to crisis, and during 2012-2016, the average healthcare spending was decreased by 3.5% annually . The overall spending in 2012 was €16,984 million and in the year of 2016 was fallen to €14,727 million which is 8.45% of GDP. In 2016, the Government Health Expenditure was €9,034.7 million, meaning 61.3% of the total.[8]

As it concerns the OOP, an ICAP analysis claim that an estimated average monthly healthcare spending of the households is €103.59, while 34.40% of the amount concerns drug therapy.[8]

As life expectancy is increased, as the live births in Greece are decreased, the population mix based on age most possible will change. ICAP estimates that though in 2003 population over 65 years age was 17.5%, it will rise to 31.5% by the year 2050. Is seems that the combination of crisis in Greece and the ageing of population makes a CEA imperative.[8]

Table 1.4: Ischemic Heart Disease and Acute-MI in EU-28

	Ischaemic heart diseases		of which: Acute myocardial infarction including subsequent myocardial infarction		of which: Other ischaemic heart diseases		Other heart diseases		Cerebrovascular diseases		Other diseases of the circulatory system	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
EU-28	170.8	93.8	66.2	31.8	104.7	62.0	103.9	78.0	93.2	78.9	76.9	67.7
Belgium	107.7	47.9	59.7	28.5	48.1	19.4	127.0	102.5	68.5	58.7	37.8	29.2
Bulgaria	250.2	153.2	108.4	49.0	141.8	104.2	471.2	346.6	405.7	314.2	206.9	162.9
Czech Republic	415.2	274.9	88.4	45.3	326.8	229.6	93.6	63.2	131.7	109.9	95.9	79.3
Denmark	114.0	56.3	47.2	22.4	66.8	34.0	81.7	49.4	77.0	63.4	51.8	37.3
Germany	200.7	103.9	82.8	40.0	117.8	63.9	125.6	101.6	69.0	60.5	83.5	80.5
Estonia	423.1	229.2	65.3	24.3	357.8	204.9	105.2	56.2	95.2	68.2	286.4	226.3
Ireland	199.9	105.3	84.7	49.2	115.2	56.0	66.7	53.9	66.8	64.5	36.8	34.6
Greece	142.5	69.0	77.3	32.2	65.1	36.8	110.5	111.9	116.3	119.5	53.1	40.0
Spain	100.3	44.3	48.5	21.6	51.8	22.7	81.8	67.1	63.6	52.1	46.9	43.1
France	76.4	30.9	32.6	14.0	43.7	16.9	91.0	60.1	51.8	41.3	41.2	30.7
Croatia	370.8	260.5	135.5	60.2	235.3	200.3	104.9	75.7	217.6	177.0	90.2	88.4
Italy	135.7	73.0	51.2	24.6	84.6	48.3	83.4	61.1	88.0	74.0	66.7	57.7
Cyprus	158.8	68.9	70.1	32.8	88.7	36.1	106.7	108.1	64.3	74.3	67.5	60.6
Latvia	614.0	349.5	90.7	42.2	523.3	307.3	110.8	54.5	306.9	244.9	111.8	80.2
Lithuania	747.5	462.6	62.9	27.5	684.5	435.2	43.5	15.6	227.9	185.7	70.4	42.3
Luxembourg	124.6	47.9	54.8	23.3	69.7	24.5	138.7	102.3	57.5	55.2	43.3	42.3
Hungary	487.3	327.5	95.0	47.1	392.3	280.5	99.4	58.2	174.9	130.1	159.8	138.2
Malta	252.1	167.1	138.0	91.4	114.1	75.7	56.6	55.7	87.7	80.1	37.7	23.6
Netherlands	89.8	43.3	50.0	27.5	39.9	15.8	126.6	94.3	68.7	64.4	41.9	29.5
Austria	239.9	137.5	81.5	37.7	158.4	99.8	101.8	84.8	65.1	58.0	86.0	82.5
Poland	181.3	93.6	63.7	27.7	117.7	65.8	239.4	149.9	119.2	93.6	194.1	154.7
Portugal	97.2	49.0	59.8	29.9	37.4	19.2	83.0	69.3	127.0	99.1	54.4	46.2
Romania	388.9	268.5	156.5	83.4	232.4	185.1	68.7	43.2	313.4	254.0	320.8	277.2
Slovenia	149.3	70.3	74.6	33.5	74.7	36.9	151.5	152.5	123.4	97.8	81.1	81.3
Slovakia	475.7	331.0	83.0	33.4	392.7	297.5	68.5	42.9	173.8	125.1	74.4	60.9
Finland	285.9	141.3	95.6	48.9	190.3	92.4	46.6	28.5	93.4	78.2	63.4	51.9
Sweden	181.1	94.0	82.2	42.0	98.9	52.1	105.8	76.6	75.5	62.1	54.9	46.0
United Kingdom	169.0	79.4	63.7	31.5	105.3	47.9	43.5	35.5	70.7	64.3	44.5	36.1
Liechtenstein	109.9	47.5	18.9	6	91.0	41.5	169.4	94.2	46.9	39.1	72.6	57.9
Norway	131.7	68.5	81.3	42.9	50.4	25.6	96.5	70.7	68.7	58.4	38.2	27.6
Switzerland	139.4	69.5	42.8	18.8	96.7	50.7	88.2	62.7	47.7	44.3	67.0	59.0
Serbia	197.1	129.0	102.2	54.4	94.9	74.5	435.5	381.7	210.4	189.0	162.3	164.6
Turkey	255.0	156.2	176.8	111.6	78.2	44.6	115.3	101.6	138.3	125.3	85.0	87.9

Source: Eurostat (online data code: hlth_cd_asdr2)

Based on Eurostat, in the EU - 28, the death rate in persons aged younger than 65 years is 45.7 per 100,000 inhabitants, while in Portugal is 34.3 per 100,000 inhabitants and in Greece 50.5 per 100,000 inhabitants. An incident that takes place and it should be pointed out, is the fact that though the Greek population seems to reach lower rates in IHD compared to the Europeans , as it concerns the Acute Myocardial Infraction (AMI) the Greeks show higher rates.

The fact that AMI is associated with increased mortality compared to Stable Coronary Artery Disease (SCAD), might be an explanation of the increased rate of deaths in Greece.

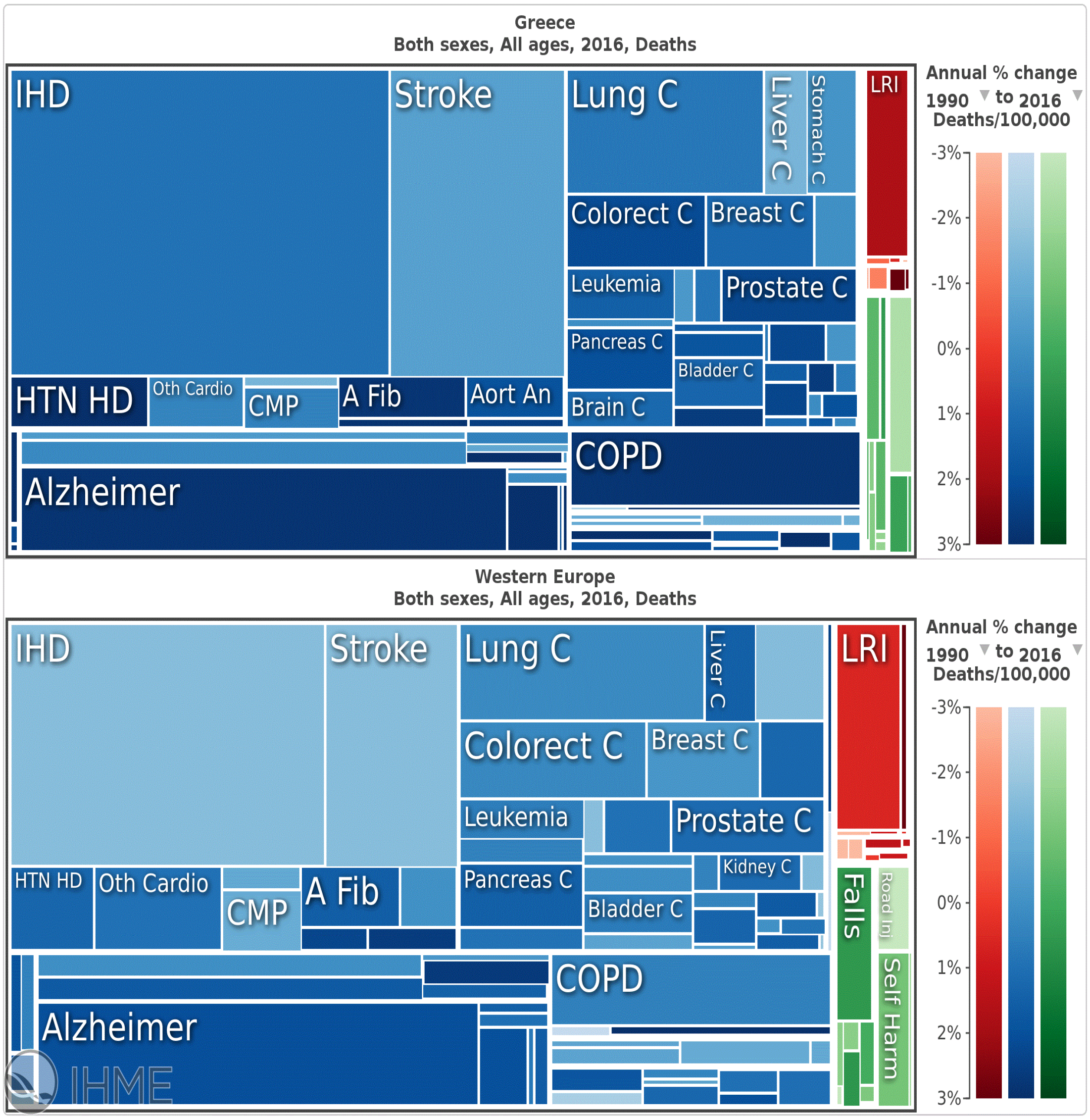


Figure 1.2: Comparison of all deaths in Greece and Western Europe[9]

Table 1.5: % of All Deaths

Disease (%) / Region	Western Europe	Greece
IHD	17.72	26.94
Stroke	7.4	12.44
AF	1.4	1.26
CMP	1.11	0.87
Hypertensive	1.64	1.65
Other CVD	2.5	1.13
Total CVD	31.77	44.29
IHD / CVD (%)	55.78	60.83

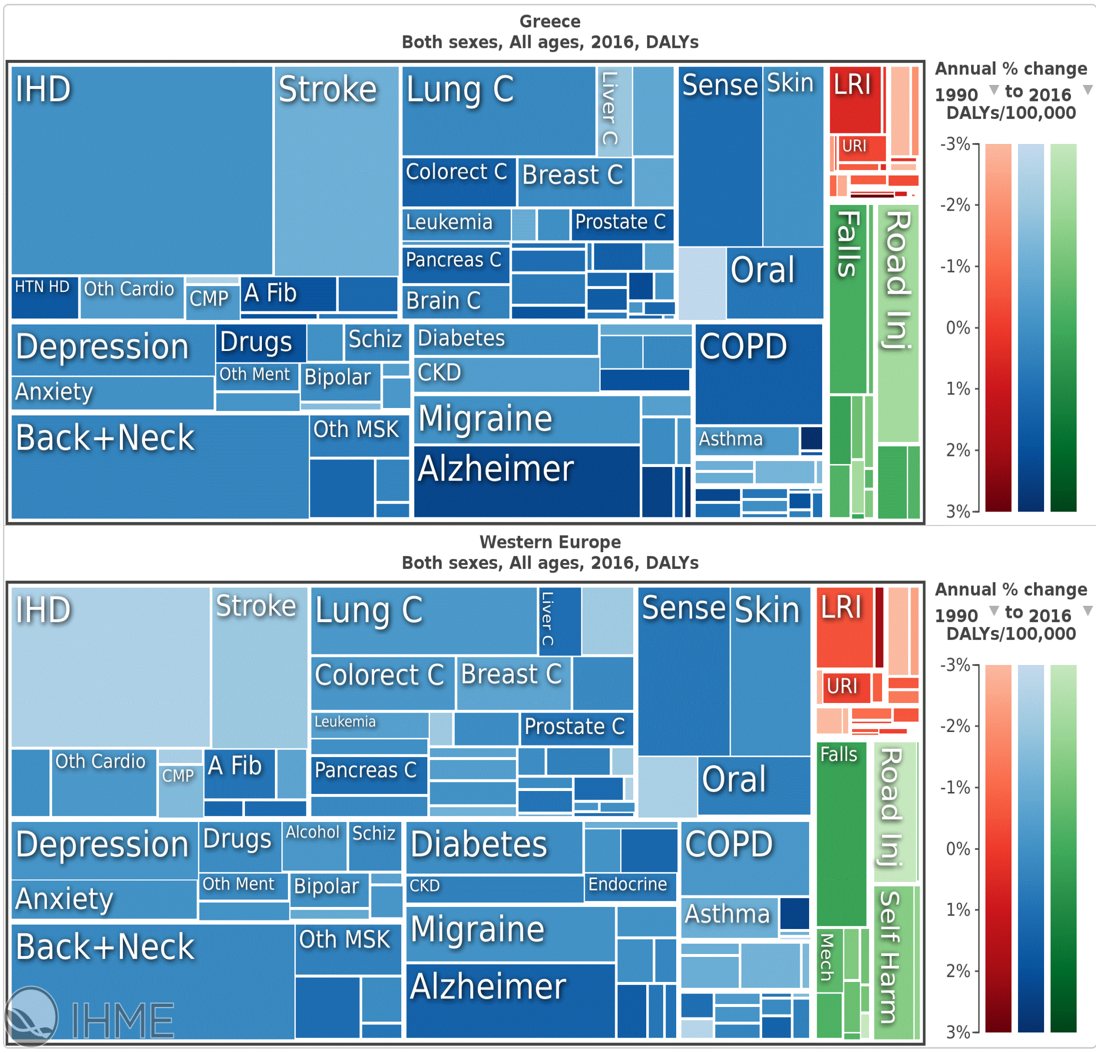


Figure 1.3:Comparison of DALYs in Greece and Western Europe[9]

Table 1.6: % of All DALYs

Disease (%) / Region	Western Europe	Greece
IHD	7.98	13.56
Stroke	3.87	6.48
AF	0.92	0.88
CMP	0.6	0.48
Hypertensive	0.69	0.75
Other CVD	1.82	1.14
Total CVD	15.88	23.29
IHD / CVD (%)	50.25	58.22

According to the Institute for Health Metrics and Evaluation (IHME) and the Global Burden of Diseases, Injuries and Risk Factors (GBD) project, sponsored by the World Bank and the Bill and Melinda Gates Foundation (2007), both CVD and its component IHD in Greece and in comparison with the Western Europe seem that the Greeks have far more “sensitive” hearts.

Western Europeans face 31.77% of all deaths caused by CVD and 17.72% caused by IHD, while the Greeks face 44.29% of all deaths caused by CVD and 26.94% caused by IHD, which is nearly 40% and 52% higher respectively.

Moreover, as it concerns the estimated number of AMIs per 100,000 inhabitants, Greece is on the top of all the EU, Greece and Portugal, when the last one seems to be at best situation of all the three.

Standardized death rates-diseases of circulatory system, residents, 2014 (per 100,000 male and female inhabitants

Table 1.7: Ischemic Heart Disease EU versus Greece versus Portugal

	EU	Greece	Portugal
IHD	264.6	211.5	146.2
AMI	98	109.5	89.7

Having a closer look at the younger patients, the 50 - 69 years aged subgroup of Greeks have an approximately double presentence in death because of IHD compared to Western Europeans, while in the 15 – 49 years subgroup the Greeks' death due to IHD is 2.5 times the Western Europeans' one.

Table 1.8: IHD of All Deaths 2016, Both sexes – GBD

Age (ys) / Region	Western Europe	Greece	Portugal
15 – 49	7.3	18.39	5.66
50 -69	12.82	23.13	9.83

Table 1.9: IHD DALYs 2016, Both sexes

Age (ys) / Region	Western Europe	Greece	Portugal
15 – 49	2.01	5.41	1.87
50 -69	7.3	13.11	5.69

It could be named as "The Odyssey of modern Greeks' work force". It is the high %GDP dept, it is the high rates of unemployment, it is the decreased public share in healthcare spending, it is the every year increasing of OOP share, it is the IHD levels, which are higher than in other European countries with similar levels of population, it is that these levels of IHD cause even higher AMIs and increased rates of death… and all the above whipping the work force of the Greeks, and as a result, the macro- and micro-economy of the country.

1.1.3 The Aegean bleeding

Assume that somebody is living on an Aegean island and faces an ischemic heart episode. What would be next? In the exception of Crete, Chios and Rhodes islands, because of hospital equipment availability, Evia and Lefkada islands, because of bridge connection to the main land, from anywhere else, either a floating or an air transportation would be required.

In 2010, in a total of 2,173 transportations, 685 concerned floating transportations while in the rest 1,488 ones, helicopters or airplanes were used. In a sum of 2,618 requests, the ones that concerned Aegean islands were 1,963, which is nearly 75% of the whole Greek island area.

As for the required treatment, 15.03% concerned Cardiology[10]

According to a five years analysis, and on regards of air transportations, in 2010, 95% of the total concerned island Greece , in 2011 and 2012, in 2013, and last in 2014, the air ones were 95.7%, 95.2% and 96.3% respectively. Regarding the air transportations which took place over Aegean compared over Ionian, it is 91.6% and 8.4% respectively.[11]

Air transportations is a “non-stop bleeding puncture site” for Greece. In the year of 2009, the annual floating transportation cost was €1,500,000. Meanwhile, the air transportation annual cost reached €17,869,965.03 for 1,646 flights.

Due to crisis, and though the Ministry of Defense and Air Force Power decided to exchange the air transportation costly models of aircrafts with less costly ones, and as a result managed to achieve a lower cost in 2013 and 2014 compared to previous years, the burden of air transportation remains high.

Table 1:10 Annual Cost per model type

Model	Annual Cost 2013 (€)	Annual Cost 2014 (€)
C 130	7,174,598	7,271,858
Super Puma AS-332	2,269,304	1,,915,668
EMB 135	418,808.4	233,924.6
A-109	392,076.8	407,074.2
AB-205	316,523.2	357,534.5
C 27 – J	1,162,855	1,328,042
Total	11,734,165.4	11,514,101.3

As it is calculated, the Average Annual Cost due to air transportation for the 2013 and 2014 time of period is €11,624,133.35.[11]

1.2. Coronary Vascular Intervention topics

1.2.1 Stent Fractures

1.2.1.1 Introduction

In order to understand what leads a stent to fracture we should first identify what we ask from a stent and which should be the mechanical and chemical properties in order to have the best possible performance of the implant.

As heart is non-static, a stent should be compatible to the vessel elasticity. How much of elasticity should be performed by the stent material and design? It should be that elastic that would be able to support the mechanical movements of the heart and at the same time have the strength to resist recoil. It should be able to support plasticity in order to be balloon expanded and remain expanded at the required diameter after the balloon catheter is deflated. In order to achieve elasticity, plasticity and high radial strength, both material and design should be considered. The higher radial strength is, the higher the resistant to elastic recoil and re-narrowing of the vessel is. However, although the stent radial strength should be high enough, it should not be that high for two main reasons. First, extremely high strength would cause trauma to the artery wall and drive to restenosis. Second, eroded stent surface combined with lack of elasticity may drive to stent fracture which is associated to restenosis and thrombosis.[12]

Table 1.11 Physical and mechanical properties of selected biomaterials.

Stent / Material	SS 316L	Co-Cr	alloyNitinol	Pt-10Ir	Ta	CP-Ti
Density (gr/cm^3)	7.95	9.1	6.45	21.55	16.6	4.5
Elastic Modulus	193	243	90	150	185	107
UTS (MPa)	670	1147	1400	340	207	300
Yield Strength	366	629	NA	200	138	200
Elongation (%)	43	46	14	25	25	30

On regards of the chemical properties of the stent material, since stents are metallic, several types of corrosion may occur such us: a) pitting corrosion , b) fretting, c) erosion, d) stress corrosion.[12]

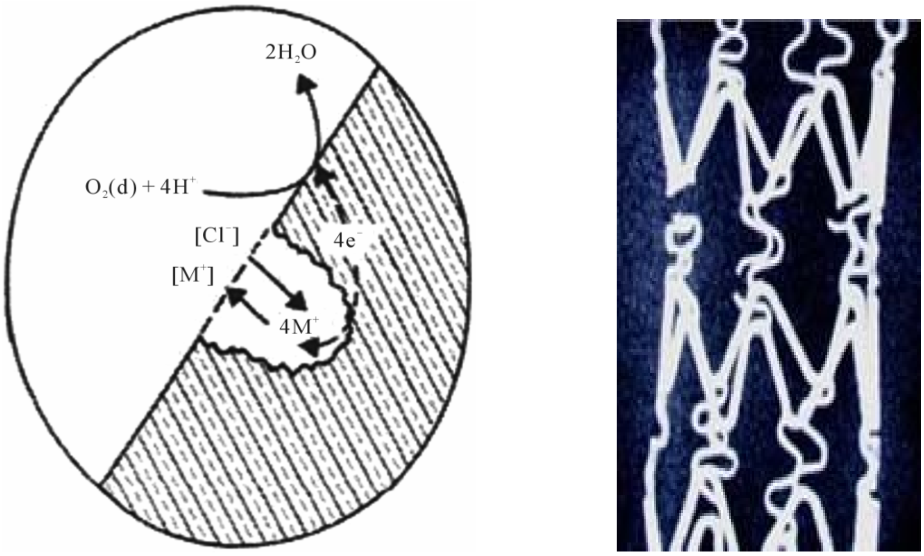


Figure 1.4: Pitting corrosion mechanism causing stent fracture

Especially stress corrosion is quite common to stents. As tensile stress comes as the result of tension and compression to each of the stent sides, electrochemical activities are triggered.

1.2.1.2 Stent Fracture Predictors

Stent fracture indicators are associated to both the stent and the vessel as following:

a) Stent material and design: elasticity, plasticity, radial strength may lead to conformability

b) Stent dimensions: Stent diameter should be in an 1:1 analog to the vessel’s one. Over-dilation of the stent may lead to strut fracture. As it concerns the length, the longer the stent is, the higher the possibility of strut fracture is.

c) Overlapping: Very long lesions are treated with 2 or 3 stents. As in the connection segments overlapping of stents is quite common, conformability to the vessel elasticity may not appear any more due to the dual metal layer.

d) Vessel characteristics: Concerning the vessel location, Right Coronary Artery (RCA) is an independent stent fracture predictor itself. In addition to this, angulations, tortuosity and high calcification may lead to increased possibility of stent fractures occurrence, due to higher mechanical forces.[13]

e) Duration of stenting: The longer the implant remains in body, the more possible is corrosion of the metal surface and mechanical stress to take place. As a result, longer duration of the implant appearance on the vessel wall leads to increased possibility of stent fracture.[14]

1.2.1.3 Stent Fracture and Clinical Outcomes

A meta-analysis of eight studies including 5,321 patients with 108 stent fractures concerning the relevance between the strut fracture phenomenon and In-Stent Restenosis (ISR) and Target Lesion Revascularization (TLR) was published in 2010. As it was reported, the mean rate of stent fracture per patient was 4.0%. The Bayesian analysis showed that lesions with SF were associated with increased ISR compared to the ones without SF (38% vs 8.2%) and TLR (17% vs 5.6%). Meanwhile, patients with ISR were analyzed and it was reported that among the ones facing ISR, SF probability was higher (12.8% vs 2.1%) and on regards of TLR (8.8% vs 2.7%).[15]

To summarize, the stent fracture phenomenon is relative to the implant, the vessel characteristics and the duration of its existence on the artery wall. As an incidence, stent fracture is associated to increased in-stent restenosis and possibility of stent thrombosis.

Table 1.12: stent Fracture Factors

Predisposing Factors	Mechanisms of SF
1. RCA Location	1. Compression, torsion, kinking, torsion, and shear stress from repetitive cardiac contractions
2. Vessel tortuosity	2. Reduced stent conformability
3. Overlapping stents	3. Hinging and buckling of stent during vessel movement
4. Increased stent length	4. Mechanical fatigue
5. Saphenous vein bypass grafts	5. Straightening of vessel after deployment of stent
	6. High radial forces
	7. Increased axial stiffness

Note: SF = stent fracture; RCA = right coronary artery.

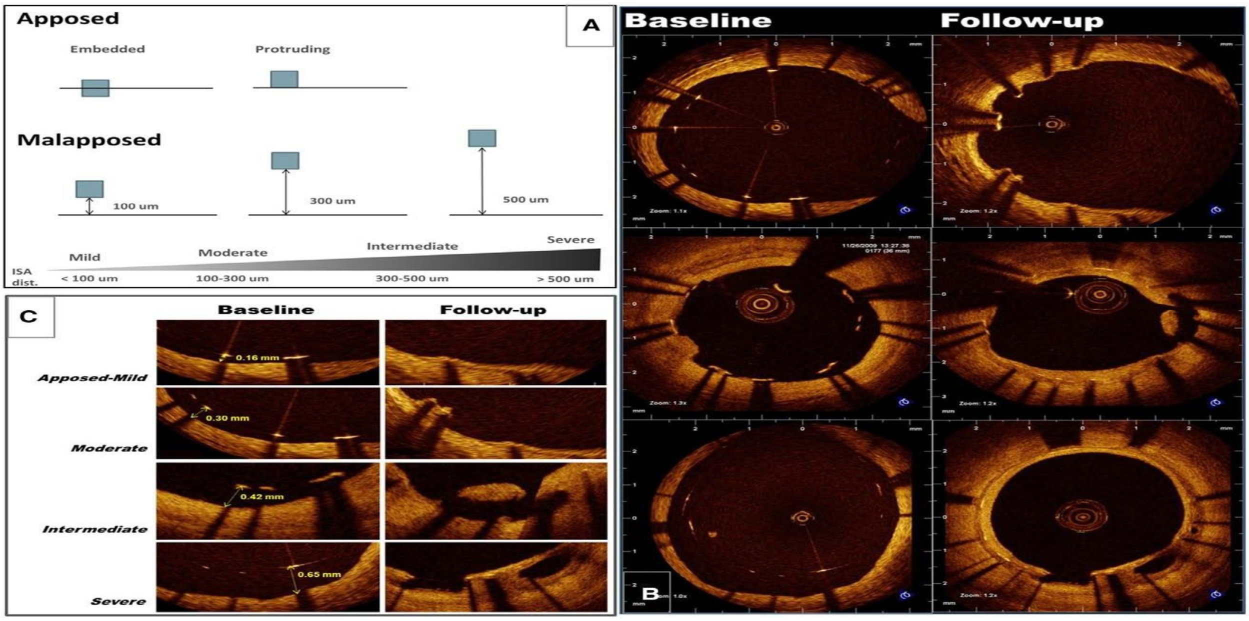
1.2.2 Malapposition and Strut Coverage

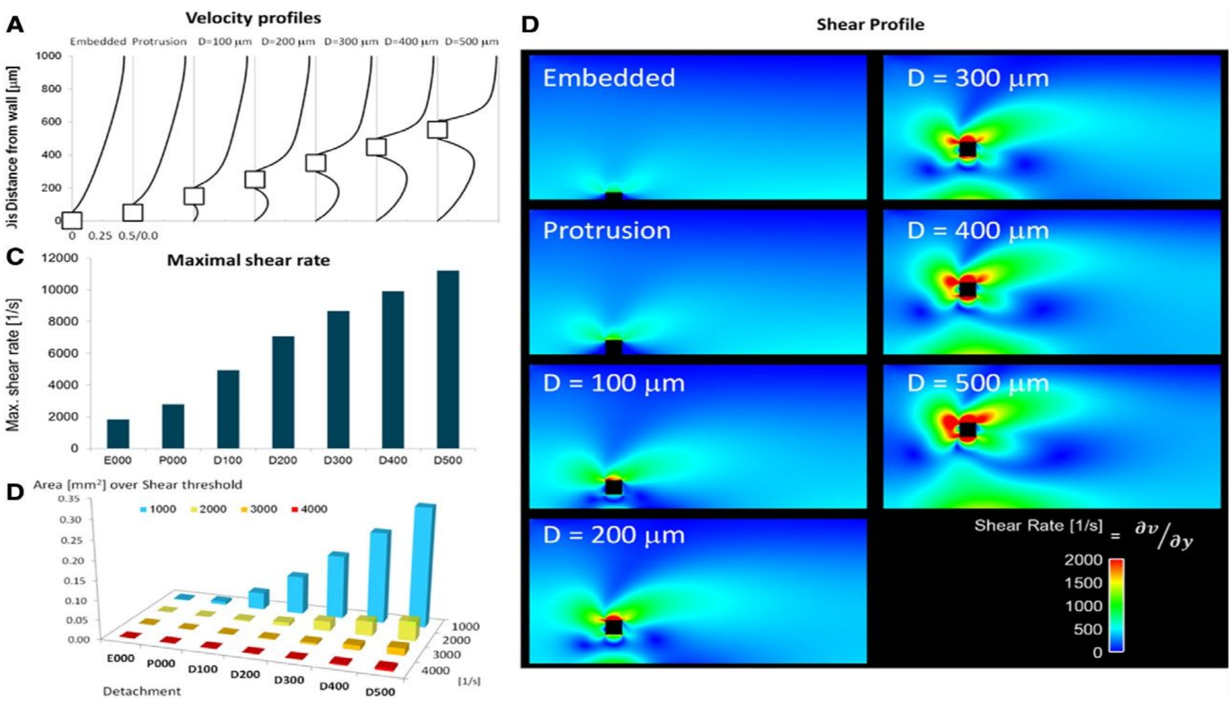
Strut malapposition is claimed to be one of the most important risk factors for stent thrombosis. In order to identify the influence of malapposition to incomplete strut coverage and re-endothelialization, a study concerning the shear rate and the blood area around struts has taken place.

The aim of the study was to categorize and analyze apposed and malapposed struts based on the distance between the strut and the artery wall and explore the blood flow velocity at each of the groups.[16]

The outcome of the analysis was the fact that the larger the distance of the wall is, the more abnormal share rate is and the blood areas are more affected. Following that, increased malapposition distance leads to higher percentage of uncovered struts and healing delaying.[16]

As it concerns the influence of malapposition to Stent Thrombosis (ST), and as Souteyrand et al. have reported based on 29 French hospital collected data, incomplete apposition of the struts may be considered as the highest frequent abnormality and concerned 34% of the studied Acute Coronary Syndrome (ACS) related to ST cases. Moreover, as it concerns the uncovered struts percentage, it was found 20%, yet, only 8% of the total were isolated connected to ST.[17]





Strut apposition			Area > shear threshold [mm2]				
	Case	Shear_max [1/s]	> 500	> 1000	> 2000	> 3000	> 4000
Apposed	E000	1828	0.76	0.00	0.00	0.00	0.00
	P000	2778	0.79	0.01	0.00	0.00	0.00
ISA	D100	4934	0.90	0.04	0.00	0.00	0.00
	D200	7062	1.04	0.10	0.01	0.00	0.00
	D300	8653	1.12	0.16	0.02	0.00	0.00
	D400	9910	1.20	0.23	0.04	0.01	0.00
	D500	11213	1.11	0.31	0.05	0.02	0.01

Figure 1.5: Impact of strut wall malapposition distance and blood flow velocity profiles[16]

In addition, in a group of 48 patients who had PCI and 2nd generation Drug Eluting Stents were implanted, an Optical Coherence Tomography (OCT) was used in order to evaluate the incomplete stent apposition.

Additionally, based on Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort consortium (PRESTIGE), in acute and subacute ST uncovered struts and underexpansion were high frequently observed. Uncovered struts were estimated to 99.3% probability, while underexpansion was reported to 44.4%.[18]

1.2.3 Neoatherosclerosis

As neoatherosclerosis phenomenon may be considered the growth of de novo atherosclerosis inside the stent due to the disease progress.

According to Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort consortium (PRESTIGE), existence of neoatherosclerosis is associated to late or very late stent thrombosis. In a sample of patients with very late ST (beyond 1 year), 59 patients of 134 in total number (44%), neoatherosclerosis was found.[18]

As it was reported in PESTO registry, the rupture of neoatherosclerotic plaque was the 2nd most frequent cause of stent thrombosis, connected to 23% of the overall ST, while 14% concerned Late Stent Thrombosis (LST) and 29% Very Late Stent Thrombosis (VLST).[17]

As the disease is not stopped but still growing, noeoatherosclerosis may be linked to very late stent thrombosis.

1.2.4 Stent Thrombosis

1.2.4.1 Introduction

Stent Thrombosis (ST) concern a thrombus generation at the site of the vessel where a stent has been implanted. Causing narrowing of the lumen of the vessel, ST may lead to ischemic episode, Myocardial Infarction (MI), Target Lesion Revascularization (TLR) or cardiac death.[19]

As it is reported by Donald E. Cutlip, in 2015, ST classification has been proposed by Academic Research Consortium (ARC) based on several topics such as timing and consequences of thrombus formation as following:[20]

Table 1.13: ARC Thrombosis Classification

Classification	Criteria
Definite	Acute Coronary Syndrome with angiographic or pathologic confirmation of thrombus
Probable	Unexplained death within 30 days or MI involving target vessel territory without angiographic confirmation
Possible	Any unexplained death beyond 30 days

Timing (after completion of the procedure)	
Early	Early: 0-30 d = acute >24 h – 30 d = sub-acute
Late	31 d – 1 y
Very Late	>1 y

1.2.4.2 Predictors of Stent Thrombosis

There are multiple risk factors which may be considered to ST and are related to the patient, the lesion, the procedure or the stent itself and are analyzed by Gill Louise Buchanan et. al.,2011 and Vinay Madan, 2013 as following:[21,20]

A. Patient Characteristics

- Diabetes mellitus (DM)
- Chronic Kidney Disease
- ACS presentation
- Dual Antiplatelet Therapy (compliance, duration, resistance)
- Current smoker
- Reduced Left Ventricular Function
- Cancer
- Thrombocythemia
- Hypersensitivity to polymer or drug
- Advanced Age

B. Lesion Characteristics

- Long segment of disease
- Small vessel diameter
- Chronic Total Occlusion
- Bifurcation lesion
- Type C lesions
- Saphenous venous graft
- Thrombus

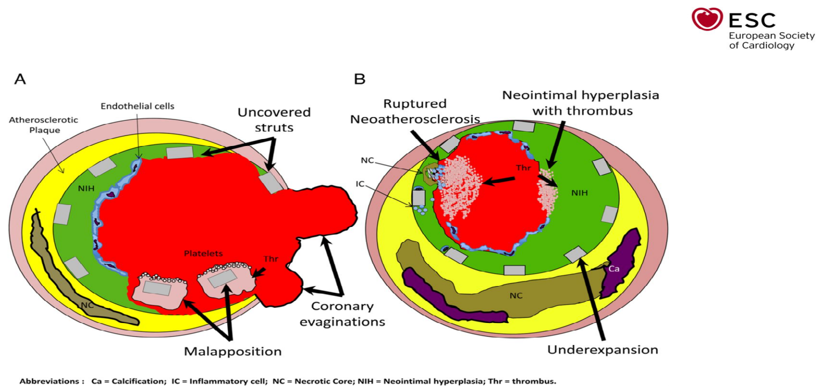
C. Procedure related

- Number of stents
- Length of stent
- Overlapping
- Stent underexpansion
- Stent malapposition
- Residual dissection
- Inflow-outflow disease
- Persistent slow flow
- Strut fracture

D. Stent Characteristics

- Type of stent (Bare Metal stent, 1st generation DES, 2nd generation DES)

- Polymer coating
- Strut thickness
- Design - geometry of stent
- Drug and elution characteristics



From: Malapposition: is it a major cause of stent thrombosis?
Eur Heart J. 2016;37(15):1217-1219. doi:10.1093/eurheartj/ehw006

Figure 1.6: "Causes of acute, subacute, late, and very late stent thrombosis. (A) Uncovered struts may be present in isolation or in the presence of malapposition, coronary evaginations, and also underexpansion (B). Malapposed stent struts are often covered by fibrin/platelet thrombus (Thr). Evaginations are defined as outward bulges in the luminal contour between struts and are a frequent finding in first-generation drug-eluting stents (DES) and less frequent in second-generation DES. (B) Underexpansion <3.00 mm² may be a cause of uncovered struts and malapposition. Late stent thrombosis can occur form underlying excessive neointimal hyperplasia, and very late stent thrombosis from neoatherosclerosis."[22]

According to Risheen Reejhsinghani et. al. 2015 and concerning the HORIZONS-AMI trial, in a sample of 3,602 patients facing ST-Elevation Myocardial Infarction (STEMI) undergoing p-PCI, a 2 years Follow-Up (FUP) showed that ST patients were noted as to be younger and have increased rates of insulin-treated DM, tobacco users, prior-MI or prior-PCI and higher baseline platelet count.[23]

1.2.5 Complex Lesions

As Complex lesions are associated to higher restenosis rates and increased possibility of stent thrombosis and/or cardiac death. The higher the complexity is, the more possible a post- procedure incidence is to take place. The scientific community, in order to indentify which cases will face higher benefits following a PCI versus a surgery, has created several scores such as SYNTAX score. SYNTAX score (Synergy between PCI with TAXUS and Cardiac Surgery) is an algorithm that is calculated by a computer based on twelve main questions-answers relative to the dominance, the total number of lesions and the involved vessel segments.[24]

Complex lesions are more challenging and as it concerns the clinical outcome less effective. As an example, as it is reported by Liefke C. van der Heijden, et. al.,2016 and with respect to DUTCH PEERS (TWENTY II) randomized trial, patients with small vessels (diameter<3.0mm) had higher TLF compared to patients with no small vessels (diameter>3.0mm).[25]

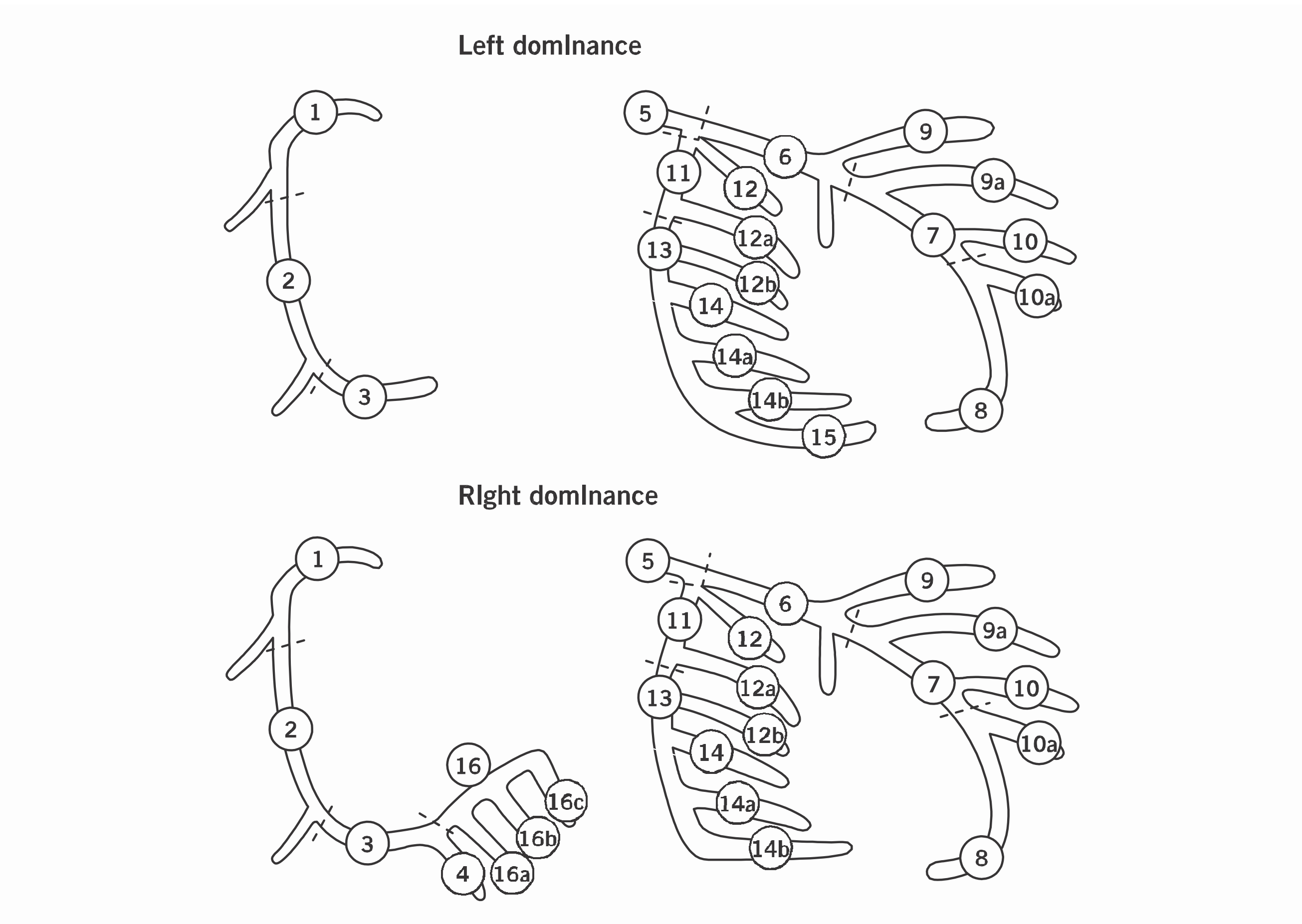


Figure 1.7: Definition of the coronary tree segments[24]

1. RCA proximal: From the ostium to one half the distance to the acute margin of the heart.
2. RCA mid: From the end of first segment to acute margin of heart.
3. RCA distal: From the acute margin of the heart to the origin of the posterior descending artery.
4. Posterior descending artery: Running in the posterior interventricular groove.

16. Posterolateral branch from RCA: Posterolateral branch originating from the distal coronary artery distal to the crux.

16a. Posterolateral branch from RCA: First posterolateral branch from segment 16.

16b. Posterolateral branch from RCA: Second posterolateral branch from segment 16.

16c. Posterolateral branch from RCA: Third posterolateral branch from segment 16.

5. Left main: From the ostium of the LCA through bifurcation into left anterior descending and left circumflex branches.
6. LAD proximal: Proximal to and including first major septal branch.
7. LAD mid: LAD immediately distal to origin of first septal branch and extending to the point where LAD forms an angle (RAO view). If this angle is not identifiable this segment ends at one half the distance from the first septal to the apex of the heart.
8. LAD apical: Terminal portion of LAD, beginning at the end of previous segment and extending to or beyond the apex.
9. First diagonal: The first diagonal originating from segment 6 or 7.

9a. First diagonal a: Additional first diagonal originating from segment 6 or 7, before segment 8.

10. Second diagonal: Originating from segment 8 or the transition between segment 7 and 8.

10a. Second diagonal a: Additional second diagonal originating from segment 8.

11. Proximal circumflex artery: Main stem of circumflex from its origin of left main and including origin of first obtuse marginal branch.

12. Intermediate/anterolateral artery: Branch from trifurcating left main other than proximal LAD or LCX. It belongs to the circumflex territory.

12a. Obtuse marginal a: First side branch of circumflex running in general to the area of obtuse margin of the heart.

12b. Obtuse marginal b: Second additional branch of circumflex running in the same direction as 12.

13. Distal circumflex artery: The stem of the circumflex distal to the origin of the most distal obtuse marginal branch, and running along the pos- terior left atrioventricular groove. Caliber may be small or artery absent.

14. Left posterolateral: Running to the posterolateral surface of the left ventricle. May be absent or a division of obtuse marginal branch.
14a. Left posterolateral a: Distal from 14 and running in the same direction.
14b. Left posterolateral b: Distal from 14 and 14 a and running in the same direction.
15. Posterior descending: Most distal part of dominant left circumflex when present. It gives origin to septal branches. When this artery is present, segment 4 is usually absent.

Lesions adverse characteristic scoring

Diameter reduction*	
- Total occlusion	x5
- Significant lesion (50-99%)	x2
Total occlusion (TO)	
- Age >3months or unknown	+1
- Blunt stump	+1
- Bridging	+1
- First segment visible beyond TO	+1/ per non-visible segment
- Side branch (SB) - Yes, SB <1.5mm**	+1
- Yes, both SB < & 1 .5mm	+1
Trifurcations	
- 1 diseased segment	+3
- 2 diseased segments	+4
- 3 diseased segments	+5
- 4 diseased segments	+6
Bifurcations	
- Type A, B, C	+1
- Type D, E, F, G	+2
- Angulation <70°	+1
Aorto ostial stenosis	+1
Severe tortuosity	+2
Length > 20mm	
Heavy calcification	+2
Thrombus	+1

“Diffuse disease”/small vessels +1/ per segment number

1.2.6 Myocardial Infarction

ST-Elevation-Myocardial Infarction (STEMI) and Non-ST-Myocardial Infarction (NSTEMI) patients happen to be one of the most challenging cases to treat. The main reasons seem to be the fact that STEMI and NSTEMI patients have to deal with an acute event followed by high mortality rates. According to J. Kanakakis,et.al.,2014 , on regards of STEMI patients, the overall in-hospital mortality varies between 3%-10.0%. As it concerns Greece, the STEMI patients treated with primary-Percutaneous Coronary Interventions (p-PCI) were 346 per 1,000,000 inhabitants, in 2010/2011. Meanwhile, the STEMI patients treated with thrombolysis were 418 per 1,000,000 and the no-reperfusion ones 289 per 1,000,000 inhabitants.[26]

Based on G.Lemesle, et.al., 2017, although in Stable Coronary Artery Disease (SCAD) a myocardial infarction may occur at 0.8% annually, the MI caused by Very Late Stent Thrombosis (VLST) is 20% of all MI and 1/3 of all STEMIs, facing very high mortality rates, approximately 18% per year.[27]

As David M. Kern, et. al., 2015, reported concerning the long-term CV risk and cost of MI survivors, high risk MI patients, who had been event free for at least 1 year, were found to be in cardiovascular risk and had increased healthcare costs for 5 years after the myocardial infarction.[28]

1.2.7 Dual Antiplatelet Therapy

According to D. Alexopoulos, et. al.,2016, based on the Global Registry of Acute Coronary Events (GRACE), which concerned 3,721 ACS patients followed for five years, the rates of post procedure death was 19% in STEMI subgroup and 22% in NSTEMI.[29] As U.S.Tantry, et. al.,2016, reports patients with a history or prior myocardial infarction, also known as “clot formers”, are in higher risk of a new event compared to the SCAD ones.[30]

At the same time, as W. J. Jang, et. al.,2018, have reported, based on the evaluation of 2,082 patients who had stent implantation in bifurcation lesions and were divided in two DAPT- duration subgroups, patients who received prolonged DAPT ≥12 months showed lower rates of death or MI in 4 years compared to the ones who had received DAPT ≤ 12 months (2.8% versus 12.3%)[31]

Several randomized trials have been published regarding the benefits of prolonged DAPT. Despite the fact that prolonged DAPT seem to be beneficial to subgroups of patients, the increase of bleeding risk should be considered.

In order to indentify which patients face high ischemic risk and prolonged DAPT would be more beneficial, and which patients might deal with bleeding events in case of prolonged DAPT treatment, the European Society of Cardiology (ESC) scientific committee has suggested relevant scores such as PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Antiplatelet Therapy (PRECISE-DAPT) score and Dual Antiplatelet Therapy (DAPT) score.[32]

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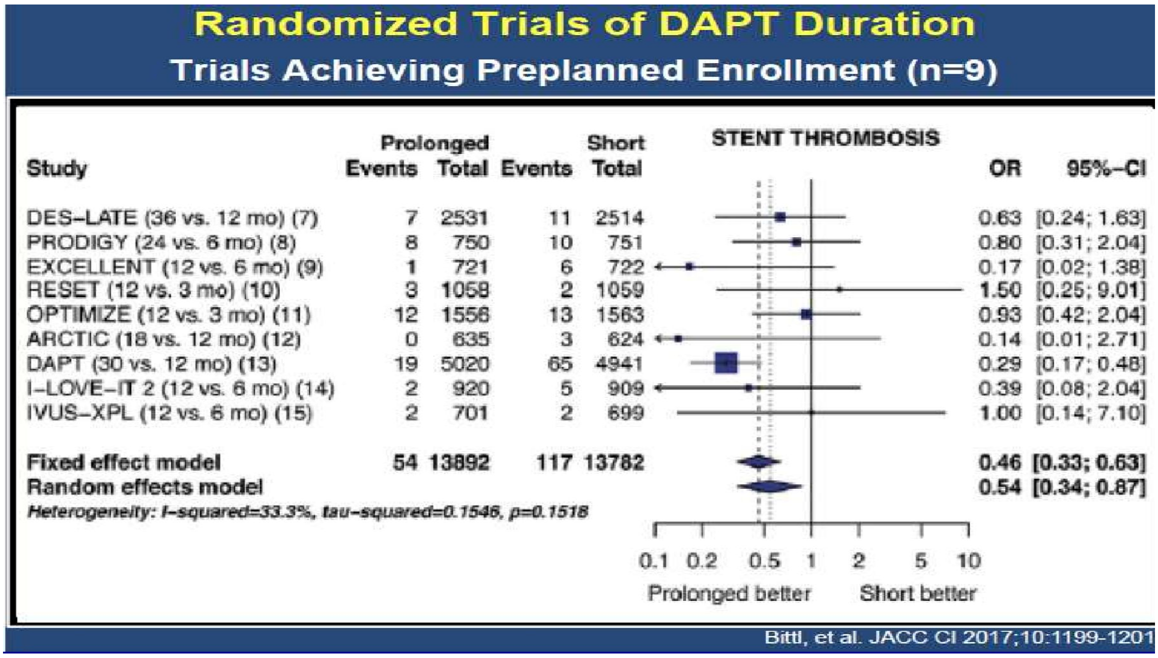
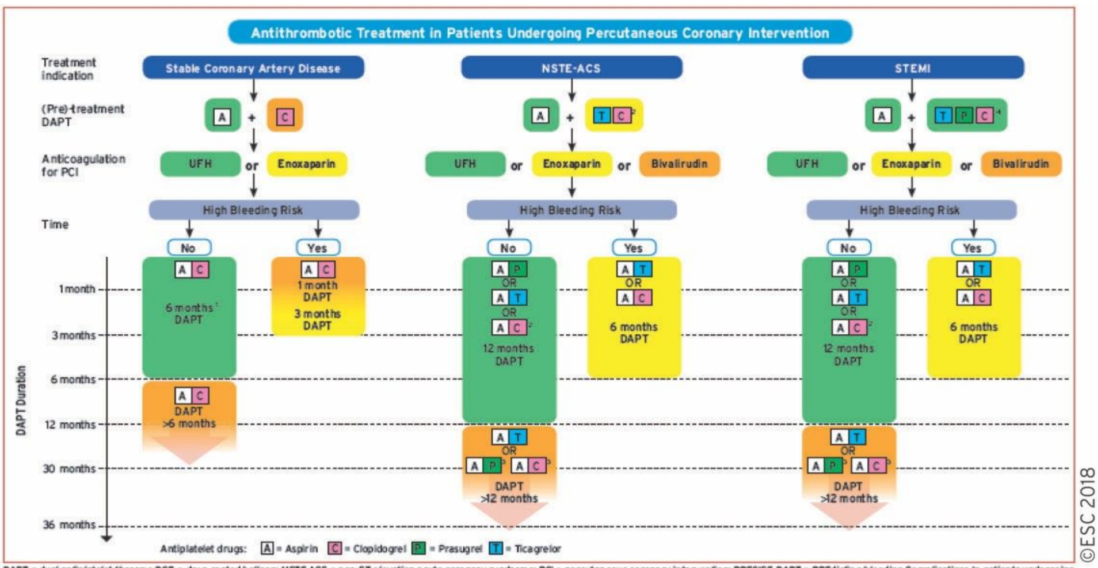


Figure 1.8: DAPT Randomized Trials

As U.S.Tantry, et. al.,2016, claim, DAPT score was developed based on clinical risk factors such as age, DM, tobacco use, history of MI or PCI, crronic heart failure, LVEF < 30% and procedural relatives: vein-graft PCI or stent diameter.[33]

Table 1.14: DAPT Scores



DAPT = dual antiplatelet therapy; DCB = drug-coated balloon; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications in patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction; UFH = unfractioned heparin.
Colour-coding refers to the ESC classes of recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).
[1]After PCI with DCB 6 months DAPT should be considered (class IIa) - [2]Clopidogrel if patient is not eligible for a treatment with prasugrel or ticagrelor; or in a setting of DAPT de-escalation (Class IIb).
[3]Clopidogrel or prasugrel if patient is not eligible for a treatment with ticagrelor - [4]Pretreatment before PCI (or at the latest at the time of PCI); clopidogrel if potent P2Y12 inhibitors are contraindicated or not available.
(For scores see Supplementary Table 4.).
High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25)

Figure 1.9: ESC Guidelines regarding DAPT European Society of Cardiology (ESC) guidelines recommend prolonged DAPT treatment to NSTEMI and STEMI patients, as long as there is no High Bleeding Risk (HBR). Even though both of the scores and ESC recommendations are quite supportive, as Prof. D. Alexopoulos, et. al.,2016, claim, physicians have to deal with a trilemma as it concerns the anti-ischemic benefits of the DAPT in post-MI patients and the potential bleeding risk which might be caused by prolonged use of each of the three P_2Y_{12} receptor antagonists (clopidogrel, prasugrel, ticagrelor). Since each of the three P_2Y_{12} receptor antagonists show to be more beneficial to different challenging subgroups of patients, DAPT treatment should be considered in depth.[29]

1.2.7 Second Generation Drug Eluting Stents

1.2.7.1 Introduction

Despite the fact that 1st generation DES managed to decrease restenosis rate, the lack of endothelialization due to polymer caused increase to stent thrombosis phenomenon. Second generation DES were the solution to that need. The polymer which is used as a carrier of the drug is more biocompatible versus the one of the 1st generation DES, the strut thickness is lower and instead of stainless steel, cobalt-chromium alloys are used. However, although in all comers population facing SCAD, the clinical studies show that ST is a rare incident, several issues remain unsolved. The stent, a foreign body, remains on the artery wall, causing allergic reactions, stent fractures potentially may cause restenosis and stent thrombosis and of course vasomotion is eliminated.

1.2.7.2 Second Generation DES Clinical Results

According to K.G.van Houwelingen, et. al., 2016, in a population of 817 patients treated for MI, a comparison between two 2nd generation DES took place. Definite stent thrombosis, at 2 years follow up, was found 1.0% vs 0.5%.[34]
As Paolo Zocca, et. al. ,2018, reported according DUTCH PEERS (TWENTE II) trial, a five years follow up of another comparison between 2nd generation DES, incidence of definite or probable stent thrombosis occurred at 1.5% versus 1.3%.[35]

As S. Kuramitsu, et. al., 2018, presented this year, on regards of long-term clinical outcomes of a 2nd generation DES, stent thrombosis at 1st year, 5th year and 7th year occurred at 0.62%, 0.74% and 1.06% respectively.[36]

If we present the pre-mentioned data on graph, we may see the acute increase of stent thrombosis rate 5years after stent implantation, which is a topic that should be considered as it concerns younger patients.

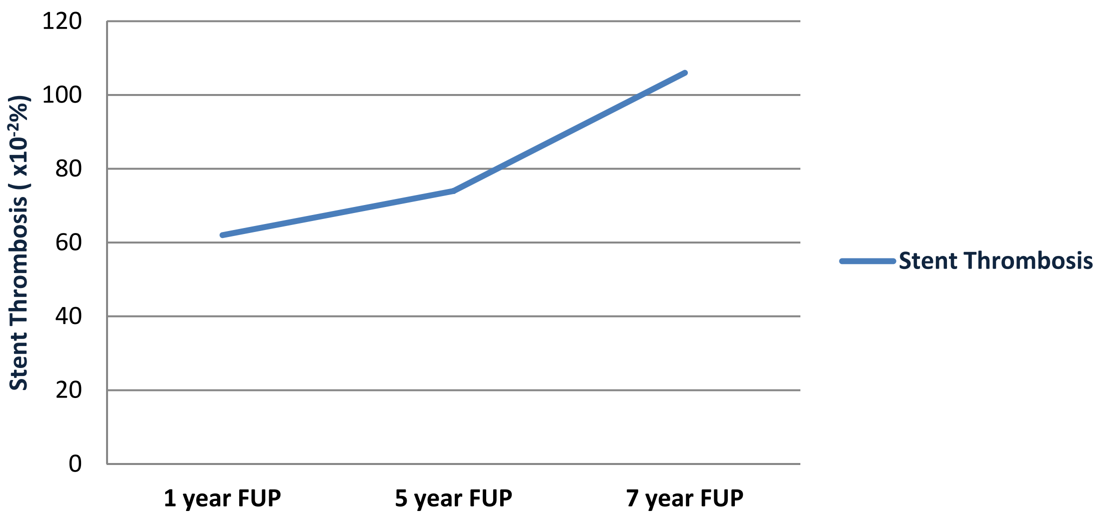
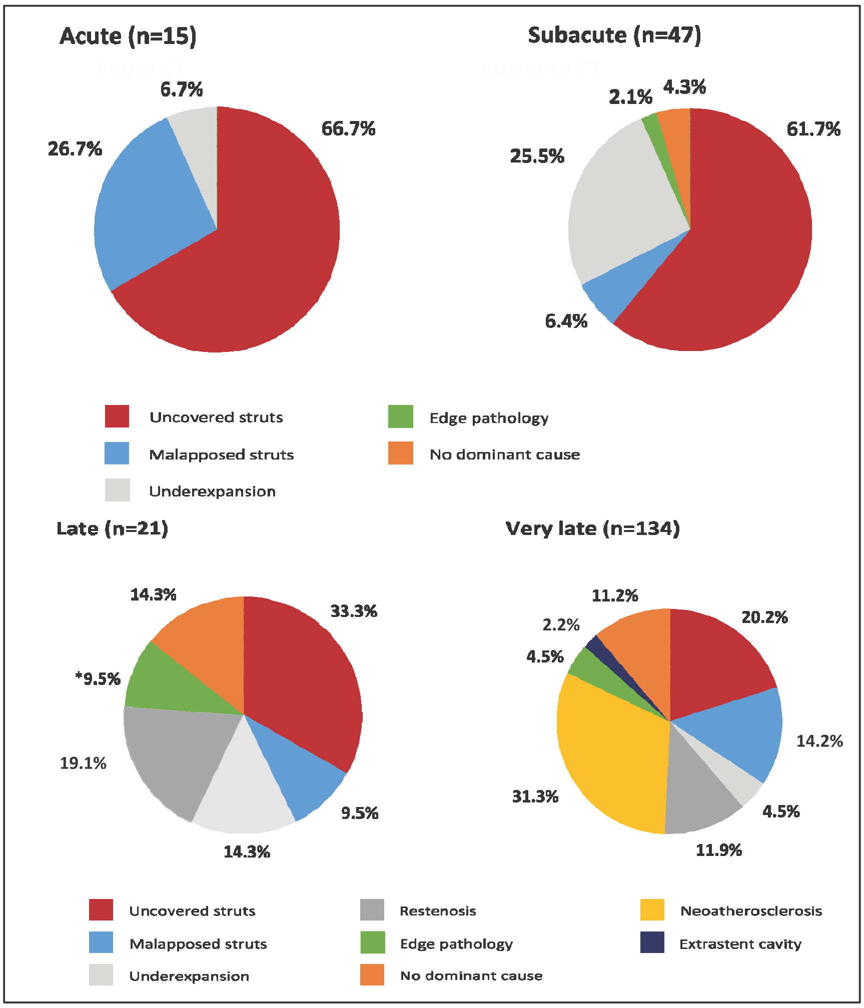


Figure 1.10: Very Late Stent Thrombosis in 2nd generation DES

1.2.7.3 Second Generation DES and Neoatherosclerosis

Bare Metal Stents (BMS) were associated to high restenosis rates. First generation DES managed to decrease restenosis, rates, however, a new threat appeared, stent related thrombosis. Second generation DES achieved to decrease stent thrombosis, especially as it concerns SCAD, yet, according to M.Joner, et. al., 2017, on regards to neoatherosclerosis, 2nd generation DES performance is worse compared to 1st generation DES. Approximately 31% of VLST takes place due to neoatherosclerosis and in a comparison between 1st and 2nd generation DES, 2nd generation DES show significantly higher neoatherosclerosis rates.[37]

As neoatherosclerosis is associated to restenosis and stent thrombosis, 2nd generation DES failure to deal with the disease progress is an issue to consider. The one step forward which has been done in order to have stent thrombosis rates decreased, was followed with one step back as it concerns neoatherosclerosis and potentially very late stent thrombosis.[37]



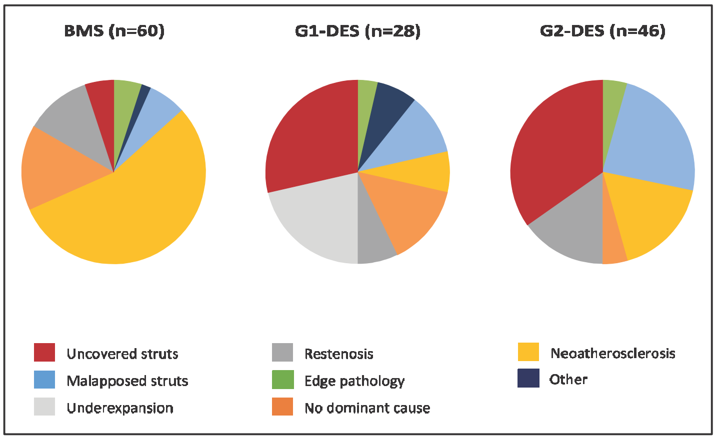


Figure 1.11: Stent Thrombosis according to time and type of stent

1.2.8 Bioresorbable Scaffolds

1.2.8.1 Introduction

Since 1st generation Drug Eluting Stents (DES) managed to decrease restenosis rates and since 2nd generation DES have significant lower levels of ST compared to the 1st generation, why there is a need of resorbable scaffold technology? The main difference between a scaffold and a stent is the fact that scaffolds are resorbed, in contrast to the stents which remain as a foreign material on the artery wall. According to Brigitta C. Brott, 2016, lack of vasomotion may lead to myocardial ischemia, thrombosis, inflammatory, atherosclerosis progression and need of repeated revascularization.[38]
Absence of metallic material and return of vasomotion seem to be promising, especially as it concerns young patients and challenging cases such as STEMI and NSTEMI, due to increased VLST rates, diffused lesions that would require very long and multiple stent implantation (full metal jacket) and bifurcation cases, in which struts of the implanted stent might cause jailed side branch.
As A. Pichard and R. Waksman presented in 2016 and with respect to the scaffold technology, the main issues which remain unsolved with the DES technology and require a more innovative treatment are:[39]

- Restenosis: remains frequent in DM and diffused lesion patients and is still an issue in small vessels
- Thrombosis: heightened in ACS, complex lesions and lesions which require long stents
- Neoatherosclerosis: frequent in BMS and DES. Potentially, the plaque may be ruptured and become the core of thrombus generation causing STEMI
- Stent Fracture: concern up to 17% of the patients and may cause restenosis, Acute-ST or aneurysm
- Lack of vasomotion: it is associated with neoatherosclerosis and it is a major issue for athletes since it may cause hyper thrombogenicity of exersice

A topic which should be pointed out is the need of absence of stent material in babies or children arteries. As a baby or child grows, the vessel size is grown in analog. In such a case, since the stent dimensions can not be updated and follow the vessel growth, a stent implantation would be just a temporary pre-surgery treatment. Resorbable scaffolds might be the ideal solution for babies and children. The bioresorbable implant would be as effective as a stent, still, it would remain in the body for as long scaffolding is needed and continuously be resorbed. Absence of foreign material would allow the vessel grow without any malapposition issues.

Bioresorbable scaffolds may be divided in two subcategories: the polymeric Bioresorbable Vascular Scaffold (BVS) and the magnesium Resorbable Magnesium Scaffold (RMS) ones.

1.2.8.2 Polymeric Scaffolds

Bioresorbable Vascular Scaffolds (BVS) are the ones that initially joined the coronary intervention market. They are well-known as "polymeric scaffolds" since the backbone is made of poly-L-lactic acid (PLLA). Although PLLA is a quite biocompatible material, the aim of early return of vasomotion and freedom of prolonged DAPT were not reached.

As it concerns the scaffold resorption time of period, the market leader of polymeric scaffolds presented a need of approximately 3 years. However, several cases were presented showing a four or even five years appear of PLLA struts and had the resorption time linked to artery wall pH. Meanwhile, the mechanical properties of the polymer were the desired ones. Elasticity, plasticity and flexibility were not favorable to the vessels requirements. Strut fracture and malapposition issues led to Scaffold Thrombosis (ScT).

According to J. J. Wykrzykowka, et. al., 2017, based on Amsterdam Investigator-initiated Absorb strategy all-comers trial (AIDA), concerning 1:1 comparison between Everolimus eluting bioresorbable vascular scaffold and 2nd generation Everolimus Eluting Stent (EES), the PLLA scaffold group were found to have definite or probable device thrombosis 3.5 times as high as the stent group, in 2 years. As a result, although Everolimus-eluting BVS with respect to TLF was non inferior, on regards to overall device thrombosis, the rates were significantly higher.[40]

Trying to identify the reasons of the failure, as it concerns the device thrombosis, several views were presented. Was it the fact that the material could not support the vessel needs, was it the long resorption time, was it the fact that the operators were not familiar to the new material – non stent like - treatment needs , was it that not all devices can treat all kind of lesions, or was a combination of all?

Regardless of the causes, the aim of shortening DAPT duration was not achieved and as it concerns the return of vasomotion, the expectations were much higher with respect to the time that it would become.
Mainly due to the pre-mentioned reasons and the fact that the causes are not clarified yet, the ESC guidelines have all scaffolds included in one category and recommend their use in clinical studies.

1.2.8.3 Resorbable Magnesium Scaffolds (RMS)

1.2.8.3.1 Introduction

Resorbable Magnesium Scaffolds are the sub-category of scaffolds made of magnesium. The fact that RMS are metallic gives them the advantage of having all the mechanical properties of DES –stent like scaffold- and be resorbed in approximately 12 months. These facts address the need of scaffolding and release of cytostatic drug, and since they are resorbed is shorter than PLLA time of period, offer earlier return of vasomotion and no need of prolonged DAPT.

1.2.8.3.2 Magnesium Alloy- the material

According to A. Pichard and R. Waksman presentation, 2016, as it concerns the chemical mechanism of Mg resorption, it is as following:[39]

$Mg + 2H_2O \rightarrow Mg(OH)_{2\,(s)} + H_{2\,(g)}$

$Mg(OH)_{2\,(s)} + HPO_4^{2-}{}_{(aq)} + Ca^{2+}{}_{(aq)} + H_2O_{(l)} \rightarrow Ca_x(PO_4)_y \cdot nH_2O_{(s)} + H_3O^+{}_{(aq)} + Mg^{2+}{}_{(aq)}$

The fact that Mg is a natural element, already existing in the human body, makes the RMS backbone quite biocompatible. Furthermore, increased Mg concentration inhibits platelet activation and prevents thrombosis, while at the same time reduces calcification of the coronary arteries.

On regards to the mechanical properties, magnesium scaffolds demonstrate higher radial strength compared to polymeric ones and stent like behavior.

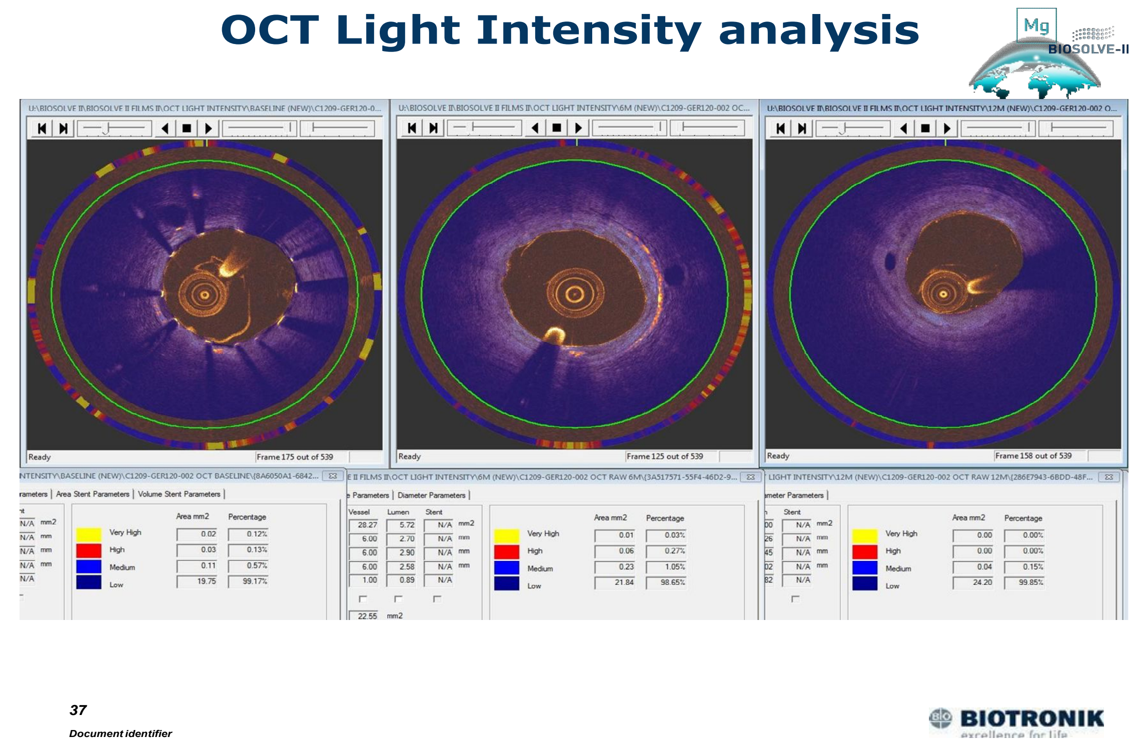


Figure 1.12: Optical Coherence Tomography of RMS[39]

1.2.8.3.3 RMS–Decrease of Neoatherosclerosis and Scaffold Thrombosis

As Prof. M. Joner presented during the Working Seminar Groups, February 2018, in Thessaloniki, magnesium scaffolds seem to reduce neointimal macrophages associated to early neoatherosclerosis compared to 316L-equivalent DES and demonstrated greater endothelial integrity.[41]

On regards to thrombogenicity, during the presentation two comparisons were presented. The first comparison concerned magnesium scaffold versus a PLLA one, which showed that there was a significant difference between the two, favorable to magnesium one.[41]

As pre-mentioned, magnesium scaffolds inhibit platelet activation, which leads to lower thrombosis. However, in order to identify if it is the design of the scaffold or the metal

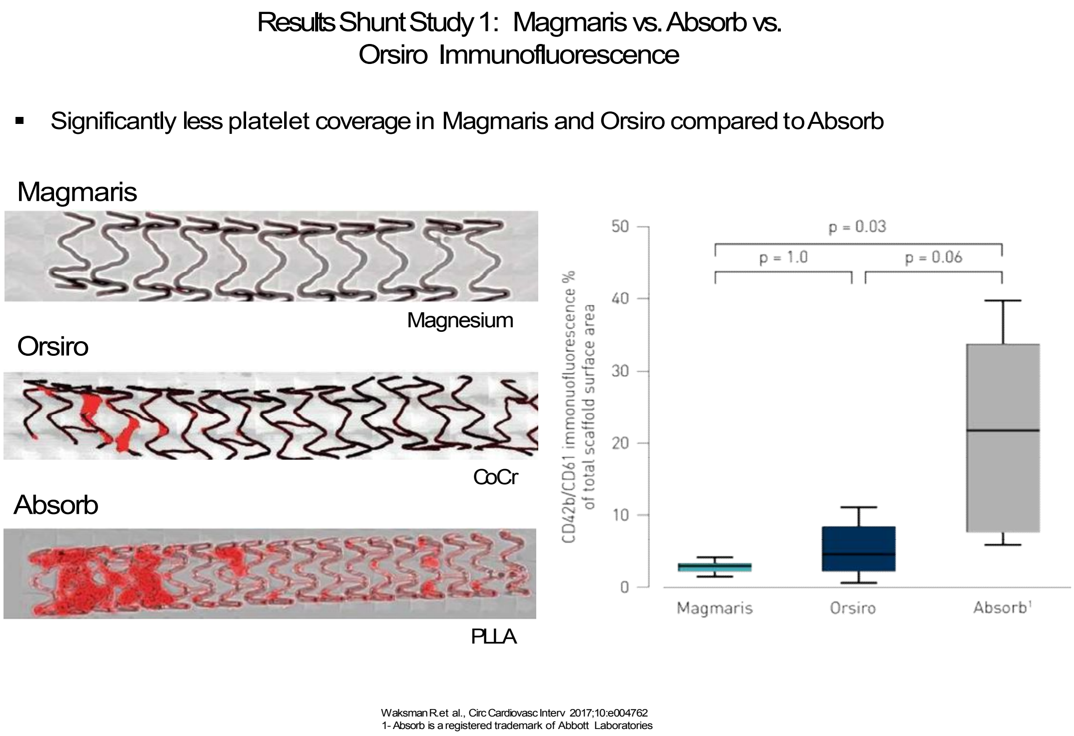


Figure 1.13: Comparison of thrombogenicity between PLLA and Magnesium Scaffolds

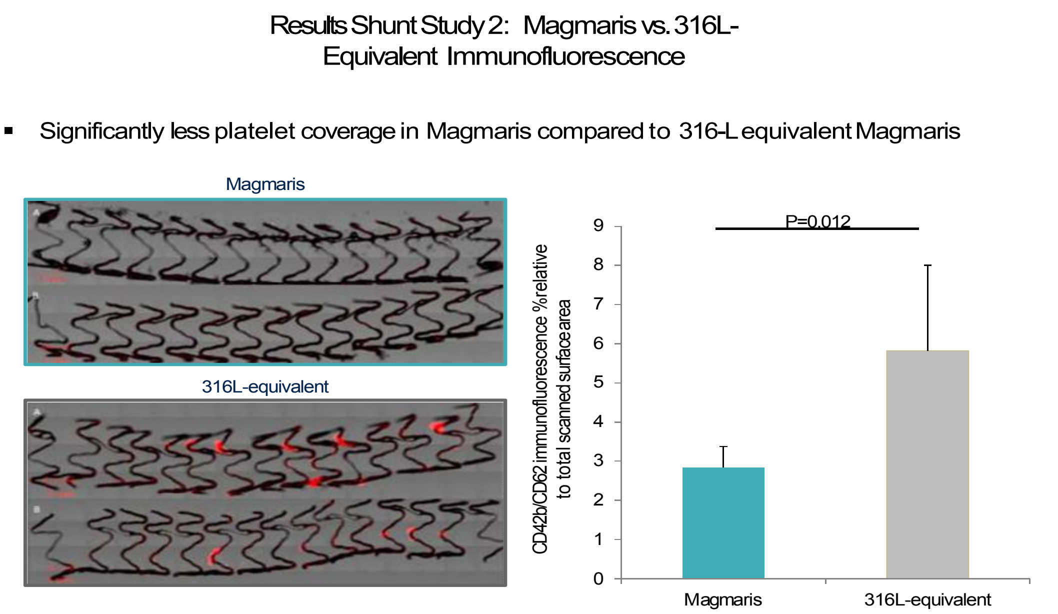


Figure 1.14: Comparison of thrombogenicity between Magnesium Scaffold and 316L-equivalent

itself which has given that low thrombus formation, a second comparison was presented. Two devices, one made of magnesium and another made of 316L-Equivalent were compared

The outcome of the two comparisons was the fact that both material and open cell design have positive effect to thrombogenicity, and that magnesium backbone may have beneficial effect to acute thrombosis.[41]

1.2.8.3.4 RMS Clinical Results

According to M. Haude, et. al.,2018, concerning the clinical outcomes of BIOSOLVE II and BIOSOLVE III, Magmaris RMS demonstrates scaffold thrombosis at 12 months follow up equal to 0%. Especially on regards to BIOSOLVE II study, as it was reported by M. Haude, et. al, at TCT 2018, definite or probable scaffold thrombosis remained at 0%.[42,43]

As it concerns more challenging cases, BIOSOLVE IV, an all comers registry, the clinical outcome of 400 patients were on same line to BIOSOLVE II and BIOSOLVE III, with an exception of one case of scaffold thrombosis due to DAPT interruption five days after the device implantation.[44]

In Greece, based on market research, it is more than 120 RMS units that have been implanted at Thessaloniki, Athens and Rio / Patras. During the National Congress 2018 of Hellenic Society of Cardiology, Dr. A. Kolyviras and V. Tzifos, Henry Dynant Hospital Center, presented an All Comers Registry which is still enrolling. Until now, the results of 58 Magnesium Scaffolds in 37 patients in 12 months follow up, were quite encouraging. Although the sample of patients concerned 85.7% complex lesions, there was only one scaffold thrombosis (acute), without the reason be identified. The very good clinical results of a such quite challenging mix of patients, as it concerns the patient and lesion characteristics, of the Henry Dynant registry, in combination with the positive feedback of all hospital centers that have already implanted RMS, is compatible to the global studies and publications, stating that Magnesium prevents thrombosis and RMS scaffold thrombosis is approximately zero.

1.2.8.3.5 RMS and Dual Antiplatelet Therapy (DAPT)

With respect to Dual Antiplatelet Therapy, ESC/EACTS Guidelines 2018 seem to share two directions. Based on the fact that the task force regarding scaffolds has suggested common recommendations for polymeric scaffolds (BVS) and Magnesium ones (RMS), the DAPT recommendations on regards scaffolds claim that the duration of post-procedure antiplatelet therapy should be at least three years.

In contrast to the above, on regards to DAPT, ESC/EACTS Guidelines 2018, recommend for both SCAD and ACS patients the following:

“In patients with SCAD treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.”[32]

“In patients with ACS treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.”[32]

Since RMS are resorbed in ~12 months, following the recommendations for post-interventional DAPT treatment, the majority of the physicians in Greece suggest approximately 1 year of antiplatelet therapy.

1.2.8.3.6 RMS and minor patients

An extremely important issue that should be considered is the need of stent implantation in babies and general minor patients with a congenital heart disease. Due to the vessel grow, a stent implantation could only be considered as temporary solution and later stent removal is required.

As Peter Zartner, et. al., 2005, have reported, a magnesium scaffold of 3.0 mm diameter has been implanted to a 26 weeks pattern baby weighted 1.7 kg. The left lung reperfusion was succeeded and the magnesium scaffold resorption was verified after a 4 months follow up.[45]

In Greece, the DRG concerning a stent implantation in patients aged < 18 years, is 3,500€.[54] Resorbable Magnesium Scaffold in such a case might be considered as the ideal solution. As the cost of RMS is affordable and no need of stent removal surgery would be, both the social benefit which concerns minor's re-hospitalization and risk of surgery and extra cost of the pre-mentioned, lead to a scaffold treatment direction.

1.3. External Environment

1.3.1 PEST

Several studies and CEA have proved the positive relationship between health and economic development of the countries and vice versa. It is seems that it is a "win – win" relation, when investment on health improves life expectancy and quality of life, which may be translated to elongation and quality of productivity and return spending, allowing re-investment on health and more.

In order to explore the cost-effectiveness and social benefit of innovative healthcare products in Greece, we should first identify Political-Legal, Economic, Social-Culture and Technological status.

1.3.1.1 Political-Legal

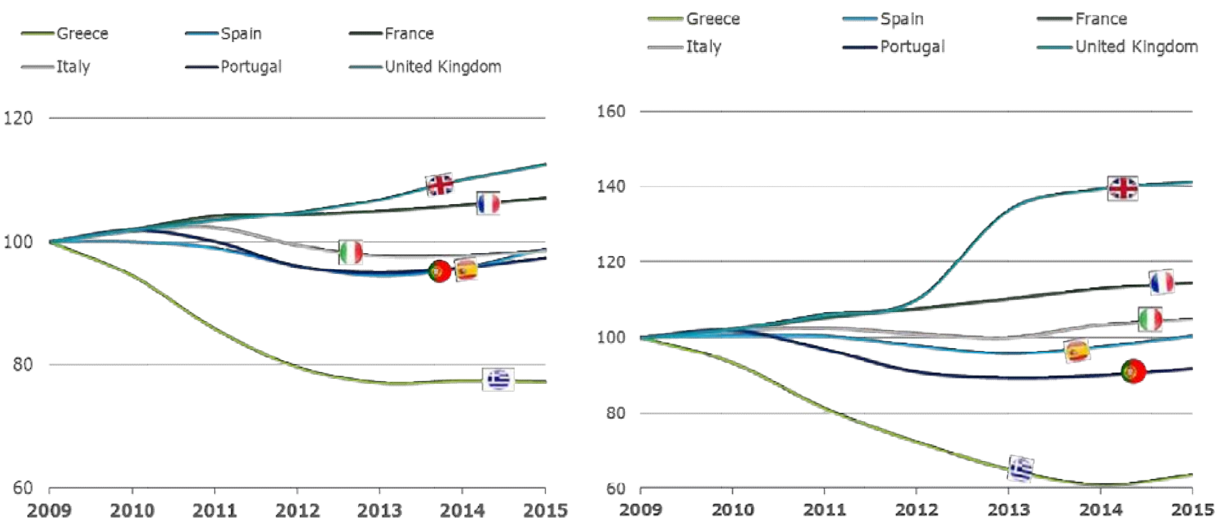
Following the economic crisis in Greece in 2010 several issues were either born or uncovered. The extremely high General government gross dept ,approximately 180% of GDP in 2016, the low GDP per capita, 63.54% of the average European one, are only the one side of the coin.

Meanwhile, on regards of competitiveness ranking, the country was evaluated as 87th in 2017, and in doing business as 67th in 2018. Instability, increased taxes rates, anti – trust status and bureaucracy, are the main causes.[7,46] .

This mix has forced Greece in a vortex with multidimensional consequences. Healthcare services is one of them. A shrank by 17.35% between 2008 – 2014 in health expenditure was required as a part of the austerity program.[47]During 2012 – 2016, an average annual reduction rate of 3.5% took place driving health expenditure in 2016 to €14,727 million from €16,984 million in 2012. Meanwhile, the public funds in 2016 concerned €9,034.7 million representing 61,3% of the total and 8.45% of GDP[8] .

Although there is a traditional relationship between GDP and health expenditures, having both following similar trends regardless the financial status of the countries, as we may see in the diagram below, health spending in Greece was precipitated due to crisis.[48]

Normalized Evolution of GDP (Real Prices) Normalized Evolution of Healthcare Expenditure



Source: Eurostat, Hellenic Statistical Authority, Deloitte analysis

Figure 1.16: Normalizes Evolution of GDP and Healthcare Expenditure

Regarding healthcare and as it concerns medical products, Greece as a EU Member State, follows all the relative European laws, including patent protection, and CE mark is mandatory. The National Evaluation Center regarding Quality and Technology in Health (EKAPY) and Price Observatory are formed in order to evaluate new technologies and offer quality in a cost effective way.

Diavgeia is the platform on which market researches and public sector expenses concerning supplies, hospital included, are uploaded, in order offers be submitted and at the same time everybody may have an overall picture.

1.3.1.2 Economic

Greece, as EU Member State and European Monetary Union one, is in cooperation with the European Central Bank. That gives the country the opportunity to import and export in Euros and without extra taxes between the country and other Member States. In 2017, the exports rate was 16.23% GDP while the imports were 28.31% GDP, giving as a result a trade balance of -21,466.8 million €, which is -12.08% of GDP.[46]

Table 1.15: European Parliament Data

	2014	2015	2016	2017[f]	2018[f]	2019[f]
Real GDP growth – *% change on previous year*						
Cyprus	-	2	3	3	3	3
Greece	0	-	-	1	1	2
Ireland	8	25	5	7	5	4
Portugal	0	1	1	2	2	2
Euro Area	1	2	1	2	2	2
GDP per capita – *purchasing power parities, Euro*						
Cyprus	22,400	23,800	24,200	n.	n.	n.
Greece	19,800	20,200	19,700	n.	n.	n.
Ireland	37,900	52,400	53,300	n.	n.	n.
Portugal	21,200	22,300	22,600	n.	n.	n.
Euro Area	29,500	30,900	31,000	n.	n.	n.
General government budget balance – *% of GDP*						
Cyprus	-	-	0	1	2	2
Greece	-	-	0	0	0	0
Ireland	-	-	-	-	-	-
Portugal	-	-	-	-	-	-
Euro Area	-	-	-	-	-	-
General government structural budget balance[1] – *% of potential GDP*						
Cyprus	3	1	1	1	0	0
Greece	2	2	4	4	2	1
Ireland	-	-	-	-	-	-
Portugal	-	-	-	-	-	-
Euro Area	-	-	-	-	-	-
General government primary budget balance[1] – *% of GDP*						
Cyprus	-	2	3	5	5	5
Greece	0	-	3	4	3	3
Ireland	0	0	1	1	1	1
Portugal	-	0	2	0	2	2
Euro Area	0	0	0	1	1	1
General government gross debt[2] – *% of GDP*						
Cyprus	107.5	107.5	106.6	97	105.7	99
Greece	178.9	176.8	180.8	178.6	177.8	170.3
Ireland	104.5	76	72	68	65	63
Portugal	130.6	128.8	129.9	125.7	122.5	119.5
Euro Area	94	92	91	88	86	84
Interest expenditure on general government debt – *% of GDP*						
Cyprus	3	3	3	3	3	2
Greece	4	3	3	3	3	3
Ireland	3	2	2	2	1	1
Portugal	4	4	4	3	3	3
Euro Area	2	2	2	2	1	1
Inflation (HICP) – *% change on previous year*						
Cyprus	-	-	-	0	0	1
Greece	-	-	0	1	0	1
Ireland	0	0	-	0	0	1
Portugal	-	0	0	1	1	1
Euro Area	0	0	0	1	1	1

Sources: all indicators are from Eurostat with extraction date 14/05/2018, if not indicated otherwise; (f): the forecasts are from the European Economic Forecast Spring 2018; (1) the source of the structural balance, primary balance and gross debt is the database DG ECFIN/AMECO; (2) the gross debt is non-consolidated for intergovernmental loans as shown in the European Economic forecasts; for the consolidated gross debt indicator, see Eurostat; (3) the current-account balance is from the European Economic Forecast Spring 2018; (4) the source of NPL ratios is the European Banking Authority Risk Dashboard - Q4; the Euro Area is defined as EA with variable composition (EA18 in 2014, EA19 thereafter)

	2014	2015	2016	2017f	2018f	2019f
Unemployment – *% of labour force*						
Cyprus	16.1	15.0	13.0	11.1	9.0	7.1
Greece	26.5	24.9	23.6	21.5	20.1	18.4
Ireland	11.9	10.0	8.4	6.7	5.4	4.9
Portugal	14.1	12.6	11.2	9.0	7.7	6.8
Euro Area	11.6	10.9	10.0	9.1	8.4	7.9
Youth unemployment – *% of labour force (15 - 24 years)*						
Cyprus	36.0	32.8	29.1	24.7	n.a.	n.a.
Greece	52.4	49.8	47.3	43.6	n.a.	n.a.
Ireland	23.7	20.5	17.0	14.5	n.a.	n.a.
Portugal	34.7	32.0	28.2	23.8	n.a.	n.a.
Euro Area	23.8	22.4	20.9	18.8	n.a.	n.a.
Current-account balance[3] – *% of GDP*						
Cyprus	-4.4	-1.4	-4.9	-8.1	-9.0	-9.7
Greece	-2.1	0.0	-0.7	-0.9	-0.4	-0.5
Ireland	1.6	10.9	3.3	12.5	11.9	11.5
Portugal	-0.3	-0.9	0.1	0.5	0.6	0.6
Euro Area, adjusted	2.5	3.2	3.6	3.5	3.4	3.4
Exports – *% change on previous year*						
Cyprus	4.2	5.8	4.0	3.4	2.3	1.9
Greece	7.7	3.1	-1.8	6.8	5.7	4.6
Ireland	14.4	38.4	4.6	6.9	5.8	4.6
Portugal	4.3	6.1	4.4	7.8	6.8	5.5
Euro Area	4.7	6.4	3.4	5.1	5.4	4.4
Imports – *% change on previous year*						
Cyprus	4.6	7.4	6.8	10.1	4.8	3.7
Greece	7.7	0.4	0.3	7.2	5.5	4.4
Ireland	14.9	26.0	16.4	-6.2	4.6	4.4
Portugal	7.8	8.5	4.2	7.9	6.9	5.6
Euro Area	4.9	6.7	4.8	4.3	5.2	4.5
Total investments – *% of GDP*						
Cyprus	11.7	13.0	17.4	21.1	n.a.	n.a.
Greece	11.5	11.5	11.7	12.6	n.a.	n.a.
Ireland	20.8	20.3	31.8	23.4	n.a.	n.a.
Portugal	15.0	15.5	15.3	16.2	n.a.	n.a.
Euro Area	19.7	19.8	20.3	20.5	n.a.	n.a.
Income Inequality (Gini Coefficient) – *Scale 0-100: 0 = total income equality; 100 = total income inequality*						
Cyprus	34.8	33.6	32.1	n.a.	n.a.	n.a.
Greece	34.5	34.2	34.3	n.a.	n.a.	n.a.
Ireland	31.1	29.8	29.5	n.a.	n.a.	n.a.
Portugal	34.5	34.0	33.9	n.a.	n.a.	n.a.
Euro Area	30.9	30.8	30.7	n.a.	n.a.	n.a.
Unit labour cost - nominal – *% change on previous year*						
Cyprus	-4.0	-1.7	-0.8	0.2	0.6	1.4
Greece	-1.8	-1.3	-0.2	0.9	0.6	0.8
Ireland	-4.4	-16.6	-0.2	-2.7	-0.9	0.5
Portugal	-1.3	0.0	2.1	1.7	1.5	1.2
Euro Area	0.7	0.4	0.8	0.8	1.4	1.0
Non-performing loans ratio in the banking sector[4] – *% of total loans*						
Cyprus	n.a	48.9	44.8	38.9	n.a.	n.a.
Greece	40.0	46.7	45.9	44.9	n.a.	n.a.
Ireland	n.a.	18.5	13.6	10.4	n.a.	n.a.
Portugal	n.a.	19.1	19.5	15.2	n.a.	n.a.
European Union	n.a.	5.8	5.1	4.0	n.a.	n.a.

In parallel, in 2017, the total investments in Greece were at lower levels compared to the EU ones, 12.6% of GDP compared to 20.5% of GDP respectively, while the bank support remained limited. This combination has driven unemployment to 20.1% of labor force compared to 8.4% in European area, in 2018, and low National Minimum Wage (NMW).[46]

1.3.1.3 Social-culture

One of the main issues that Greece has to deal with is the decrease of births. As population in Greece is ageing, the rate of live births in comparison to deaths is not positive. As the rate of population older than 65 years rises from 17.5% in 2003 to approximately 23.7% in 2030 and 31.5% in 2050 , the absolute number in live births of 2016 was 92,800 and on regards of deaths 118,800. Meanwhile, the rates in EU were 5,114,100 and 5,130,000 respectively.[8,6]

Due to increased rates of unemployment, the rate of population facing poverty was approximately 21.4% in 2015.[7] Emigration of high educated professionals has taken place as a brain drain causing population ageing and loss of valuable workforce.

High Body-Mass Index (BMI), smoking and use of alcohol are the main risk factors for several diseases. Urbanization, lifestyle and global food industries rise, in contrast to the traditional healthy Mediterranean diet, burden the population health status.

1.3.1.4 Technological

Technology is associated with R&D. Although the last years, political efforts for improving innovation have taken place, yet, the major of the investments are still based on private companies concerning new products and technologies, which quite often quit their efforts due to bureaucracy or lack of capital.[49]

On regards of transportations, we might claim that Greece is in a beneficial position, being at the Northern-Eastern side of EU, close to Asia and Africa, and being able to use all of the transportation options, meaning by air, sea and main land.

Concerning the energy sources, the country joins all the available ones and several companies, and new established companies offer attractive contracts.

The country of Greece has quite high levels in telecommunication infractures. The premium level of University education combined with the innovative mentality set up a high quality substrate and status. As it concerns healthcare services, a new data center will be installed and approximately 11 million of Greeks will be able to be served, while the data may be also used for research and political strategies.[50]

1.3.2 Task Environment

Task environment is a group of firms which may produce and/or supply similar products or services and any other engaged party that may influence the progress or have interests on the results of the procedure.

In this analysis as Task Environment will be the Coronary Vascular Intervention also known as Percutaneous Coronary Intervention (PCI) field which concerns non surgery catheterization in coronary arteries.
We will use Porter's Approach in order to identify the Forces that drive the industry competition and have influence to the Task Environment.[51]

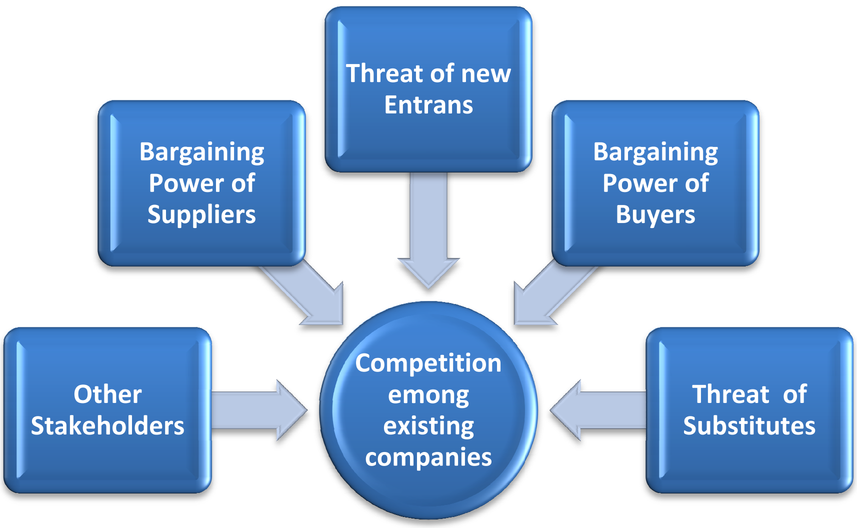


Figure 1.17: Porter - "5+1" forces

Although low cost companies are active in the Greek market, because of the low Market Share they achieve in PCI products, low cost firms will be excluded from the analysis.

1.3.2.1. Competition among existing companies

A. The number of firms and their ability to produce high quality technology products drives them to similar actions.
B. The majority of the products join the stabilization or maturity phase in the cycle of life. As a result, and in order to increase their Market Share (MS), companies face quite strong competition.
C. The economic status of the companies varies. However, the majority of the firms have the ability to share high budgets on R&D and Marketing, and as a result, be innovative and have both themselves and the market refreshed.
D. There is a differentiation between the firms regarding the distribution channels. Companies working directly have higher margins compared to the dealers and follow different strategy approach to the market.
E. Jumping from one product category to other is not impossible.

The strength of competition is enhanced by marketing activities, promotion of the products and services and reliability of the company on regards of quality and supply.

A topic which should be pointed out is the Price Observatory existence which although is a quite useful tool, it may also cause a delay to innovative products entrance the market.

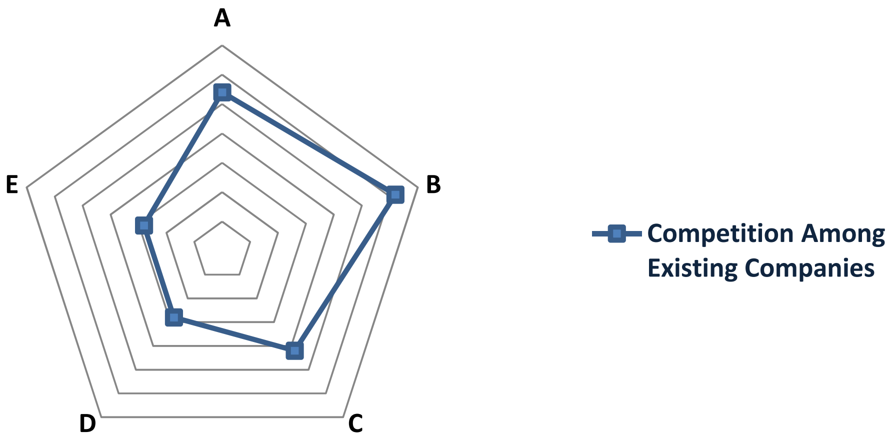


Figure 1.18: Competition Among Existing Companies

1.3.2.2. Threat of New Entrants

A. The capital requirements are quite high due to the need of existing stock and high skilled professionals. The complexity and delay of the payment terms is an additional issue and the combination creates of the pre-mentioned rises financial barriers to new entrants.
B. Due to high capital requirements and long time period of Return of Investment (ROI), non manufactures should work based on economies of scales, which is quite difficult for new entrants because of low market share.
C. As it is already mentioned, new entrants, non manufactures ones, have lower margins than manufactures that working directly submit more competitive offers.. In that case dealers either manage a small market share or work in low profitability.
D. Quality certificates should not be considered as a barrier for new entrants.
E. Price corrosion is the tool the majority of firms follow in order to achieve higher market shares.
F. Exit barriers are not unaffordable.

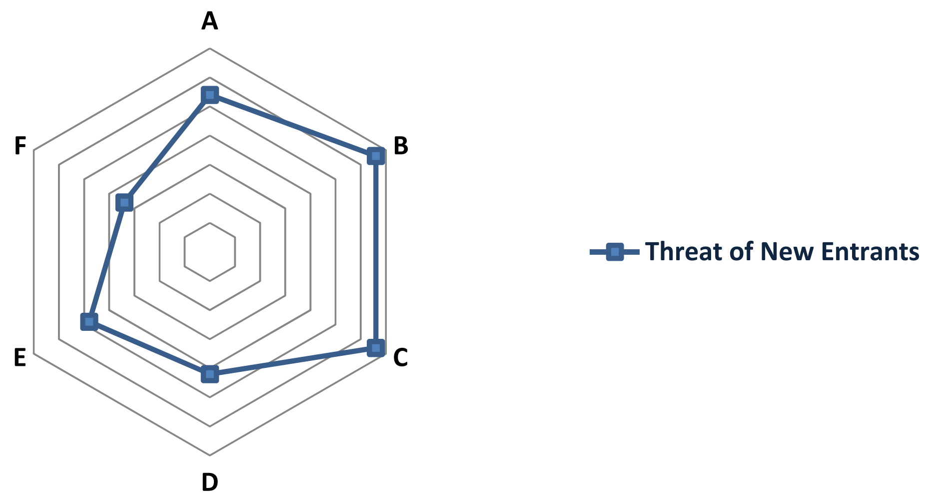


Figure 1.19: Threat of new entrants

1.3.2.3. Bargaining Power of Suppliers

A. The number of the suppliers is not small enough so to products' prices and payment terms not be negotiable.
B. As the buyers sizes vary and due to strong competition, suppliers bargaining power is weakens.
C. Differentiation between the products is possible. However, it requires investment and time consuming process, which enhance the suppliers bargaining power.
D. Forward integration strategy may not be attractive due to market complexity.

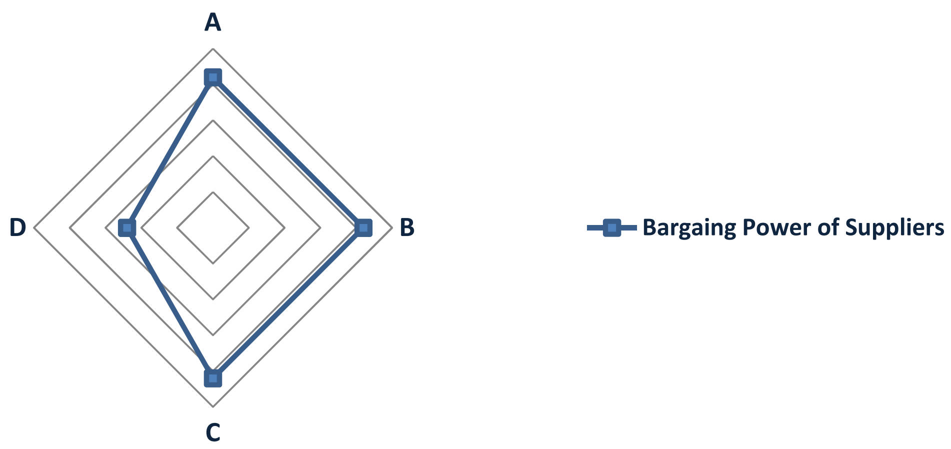


Figure 1.20: Bargaining Power of Suppliers

1.3.2.4. Bargaining Power of Buyers

Before starting the analysis concerning the bargaining power of the buyers we should identify the parties.
In Coronary Vascular Intervention buyers could be:

- Physicians
- Hospitals
- Insurance Healthcare Systems (Public)
- Private Insurance Companies
- Ministry of Health
- Ministry of Defense (Military Hospitals)
- Ministry of Education (University Clinics)
- Funds owing Private Clinics
- The State, inhabitants included
- Distributors

As it concerns the bargaining power of the buyers, it is as following:

A. The volume and the power of the centers vary. The higher the volume is, the power of the buyers is enhance. The payment terms may be considered as independent factor on regards of price negotiation.
B. As the number of suppliers is not small and competition is strong, the bargaining power is increased.
C. The environment may allow differentiation of the products as long as they have proved their superiority. In this case the bargaining power of the buyers weakens.

1.3.2.5. Threat of Substitutes

In the Coronary Vascular Intervention environment the main substitutes are:

A. Drug Treatment

B. Coronary Artery Bypass Grafting (CABG)

C. Stents

Safety and efficacy in combination with cost effectiveness are the major criteria of choice.

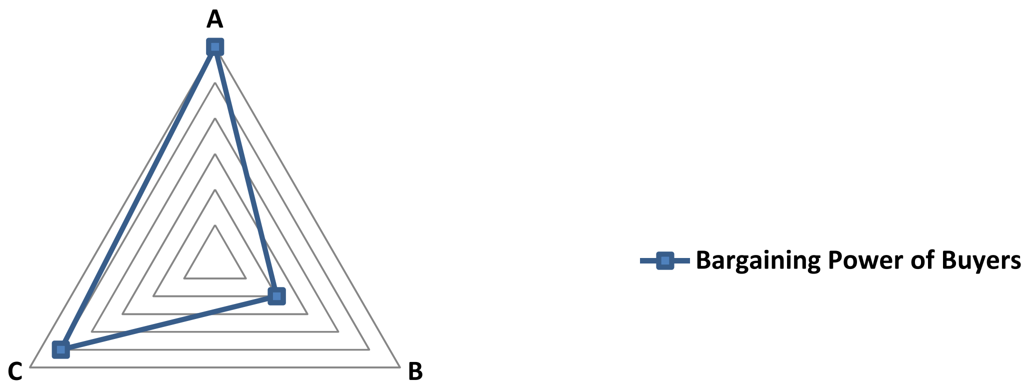


Figure 1.21: Bargaining Power of Byers

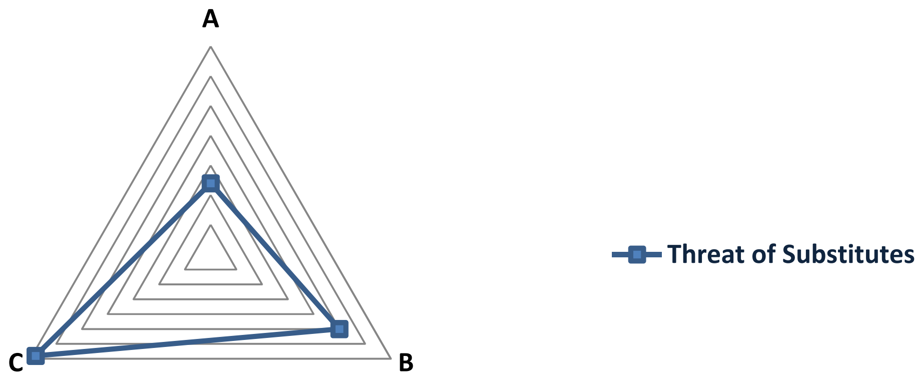


Figure 1.22: Threat of Substitutes

1.3.2.6. Other Stakeholders

Other stakeholders who are engaged are the following:

- The firms' stakeholders
- Universities
- Independent companies such as mechanical testing companies and research centers
- Hellenic Cardiology Society (HCS) and others
- Quality Committees
- Customs
- Agencies
- Media

Summarizing, as it concerns the Task Environment of Coronary Vascular Intervention, competition among existing companies, bargaining power of buyers and threat of substitutes are quite strong, however, the task environment remains attractive.

As a result, the combination of all forces give the picture of the task environment as following:

A. Competition Among Existing Companies

B. Threat of New Entrants

C. Bargaining Power of Buyers

D. Bargaining Power of Suppliers

E. Threat of Substitutes

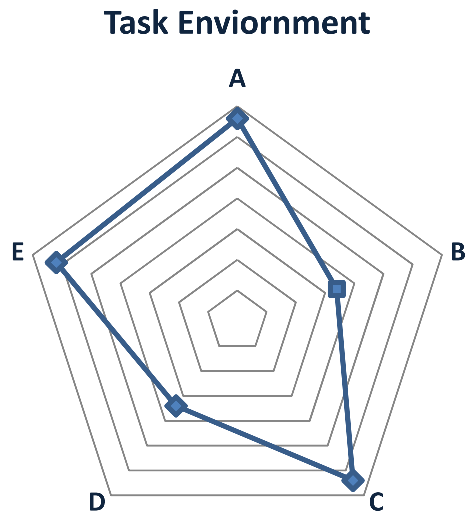


Figure 1.23: Task Environment

In order to conclude, with regard to the task environment, competition among the companies, bargaining power of buyers and threat of substitutes are the main to consider.

1.3.3 Internal Environment

Concerning the internal environment, we will explore the Strengths and Weaknesses, Opportunities and Threats of RMS firms. During the SWOT analysis and in order to identify the most important factors, we should consider that 2nd generation Drug Eluting Stents (DES) companies share above 80% Market Share. On regards of pricing, RMS market price is much higher than the 2nd generation DES one.

Strengths

Brand name associated to quality and reliability

Healthy financial status

Innovative

Globalized-risk spreading

Production in countries with high competitiveness and quality standards

Weaknesses

- High production cost
- As long as RMS joins the initial phase, the market price is high, the company less competitive and the market share low

Opportunities

- Increase of IHD in younger patients
- Urbanization and unhealthy diet
- Increase of diabetes mellitus rate

Threats

- Decrease of health expenditure-Price sensitive market
- Payment delays and payment terms
- Absence of DRG and Price Observatory Category - complex and time consuming process
- Strong competition
- High bargaining power of buyers

Based on the Strengths, Weaknesses, Opportunities and Threats, a SWOT analysis template will be made. In column 1, we will list the most important of the pre-mentioned factors. In column 2, we will weight each of the factors as 0.0 the non-important and 1.0 the most important ones (total = 1.00) and on regards the impact the factor has on the companies' performance.
In column 3, we will evaluate the companies' performance to the factor as 5.0 the exceptional and 1.0 the limited. In column 4, we will multiply the rates of columns 2 and 3 in analog, and in column 5, we will have our comments respectively.[51]

Table 1.16: SWOT Analysis of companies on regarding RMS

Strategic Factors	Weight	Rating	Weighted Score	Comments
Innovation	0.15	4.5	0.68	Need of randomized clinical results
Brand Name	0.13	4.3	0.56	
Cost Production	0.09	2.2	0.2	Automation should be considered
↓ of Mean Age IHD	0.12	4.5	0.54	
↓Health Exp.	0.13	2.1	0.27	The price-volume relation should be consider
DRG/Price Observatory	0.14	2.1	0.29	A request and a CEA should be submitted
Strong Competition	0.15	2.8	0.42	Identify the target group and position the product
Power of Buyers	0.09	3.3	0.3	Have the MoH enganged
Total Performance	1.00		3.26	

RMS companies seem to have manage well in presentation the product in the Greek market in that initial phase of the technology, yet, they haven't manage to achieve a that fruitful business and an acceptable Market Share, due to DRG and Price Observatory category absence, decrease of health expenditures, strong competition and high production cost which drives to high market price.

Chapter 2

Indirect Cost - Method and Estimations

2.1. Estimation of PPYLL for the year 2050

The EU population in 2016 was 510,278,700 while in Greece were 10,783,700 and in Portugal 10,341,300, having both Greece and Portugal shares nearly to 2% of the EU inhabitants.

As discussed, and on regards of CVD, the Potentially Productive Years of Life Loss (PPYLL) for Portugal and for the year 2008 was 12,909 and it is estimated approximately 10,052 for the year of 2050 in ages 35 – 64 years.

Based on Table 2.1, in 2014 the estimated rates of IHD per 100,000 inhabitants in Portugal was 146.2, while in Greece was 211.5, increased by of 44.66% compared to Portugal. As it concerns the AMI, the rates per 100,000 inhabitants for Portugal for 89.7 and for Greece 109.5, increased by 22.07%.

Assuming that both Greece and Portugal have equal populations and based on calculations, as it concerns Portugal, 15,442 inhabitants face IHD and on regards of the Greek inhabitants, it is 22,338.

Table 2.1: IHD of All Deaths 2016, Both sexes - GBD

Age (ys) / Region	Western Europe	Greece	Portugal
15 – 49	7.3	18.39	5.66
50 -69	12.82	23.13	9.83

Table 2.2: IHD DALYs 2016, Both sexes

Age (ys) / Region	Western Europe	Greece	Portugal
15 – 49	2.01	5.41	1.87
50 -69	7.3	13.11	5.69

Meanwhile, the Figure 2.2 shows that the highest shares of DALYs due to CVD, concern IHD and stroke, with the IHD covering approximately more than 55% of the total, in ages >35 years old.

Based on the data below, we create a multiplier that allows us to transform data from Portugal to Greece, as following:

Coefficient = (Rates in Greece) / (Rates in Portugal)

Table 2.3: % IHD of all deaths

	Greece	**Portugal**	**Coefficient**
15-49	18.39	5.66	3.25
50-69	23.13	9.83	2.35
Average			2.8

Table 2.4: % IHD in all DALYs

	Greece	**Portugal**	**Comp. Indicator**
15-49	5.41	1.87	2.89
50-69	13.11	5.69	2.30
Average			2.6

Multiplier = Mean rate of coefficient = 2.7

In 2050, PPYLL in Portugal will reach approximately 10,052 due to CVD. Since based on Figure 2.2, more than 55% of CVD concern IHD, we may estimate that PPYLL due to IHD in Portugal, in 2050, will be > 5,529.

Using the multiplier 2.7 in order to transform PPYLL results from Portugal to Greece, the estimated PPYLL in Greece due to IHD in workforce, for the year 2050, is 14,927.

As the Scientific Committee regarding the National Tender in Greece claims that approximately 4.14% of all stents should be scaffolds, and since the estimated rate of scaffolds RMS per patient is 1.6, we may claim that the estimated gain due to RMS use, in 2050, for the workforce in Greece, in PPYLL, is 386 years.

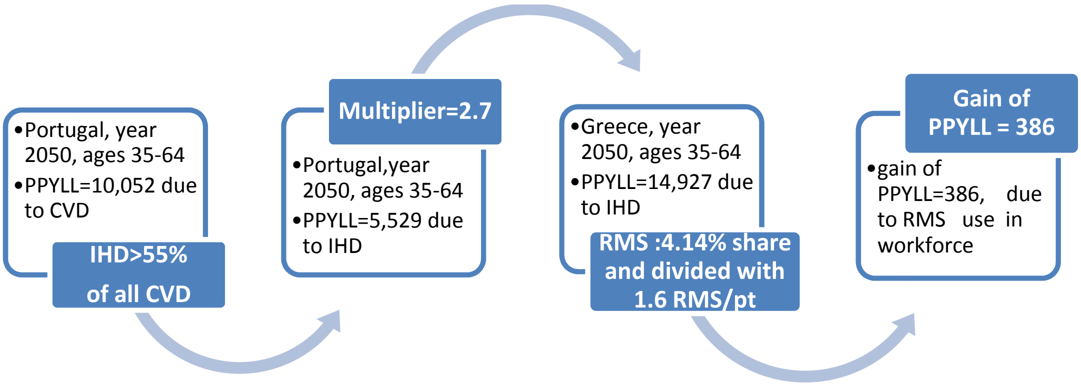


Figure 2.1: Gain of workforce PPYLL by the year of 2050, due to RMS use

2.2 Estimation of DALYs

In order to estimate DALYs we use data based on ELSTAT:

Table 2.5: Population of age-subgroups based the following template

Population			
	2011		
Ages	Sum	Male	Female
Overall	10.816.286	5.303.223	5.513.063
0 - 9	1.049.839	537.220	512.619
10 – 19	1.072.705	552.173	520.532

20 – 29	1.350.868	696.744	654.124
30 – 39	1.635.304	827.542	807.762
40 – 49	1.581.095	781.112	799.983
50 – 59	1.391.854	677.018	714.836
60 – 69	1.134.045	543.421	590.624
70 – 79	1.017.242	456.247	560.995
80 +	583.334	231.746	351.588

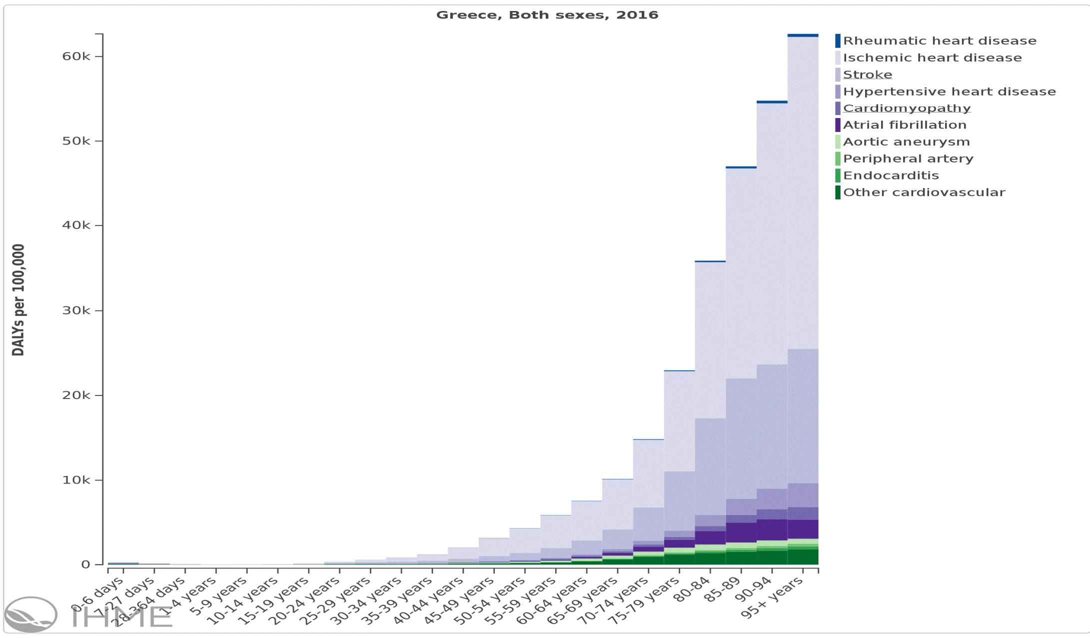


Figure 2.2: Cardiovascular Disease components and Ischemic Heart Disease DALYs rates per 100,000, per age groups

Continuously, we multiply the rate respectively and find DALYs in Greek age-subgroups and in total.

We assume that population number in total, population rates facing IHD, deaths and DALYs due to IHD remain approximately the same since 2011 and that all of the population dealing IHD is treated with stents, regardless thrombolysis pre-treatment.

Based on National Tender Scientific Committee, 4.14% of a total of 24,744 stents should concern scaffolds. We assume that due to the RMS benefits, a 4.14% gain in DALYs will take place, and we calculate this gain in the workforce subgroup.

(4.14%) X (112,098 DALYs) = 4,641 DALYs

Since one patient may have 1 or 2 or more scaffolds implanted, and since DALYs concern the Disability-Adjusted-Life-Years of persons, regardless the number of scaffolds, we calculate based the estimated average rate of RMS per patient, which is approximately 1.6 RMS / patient, the final DALYs are:

Table 2.6: Estimated DALYs due to IHD per age-subgroup

Ages	DALYs/100,000	Est. Population	DALYs due to IHD
30-34	484	817,652	3,957
35-39	763	817,652	6,239
40-44	1,309	790,548	10,348
45-49	2,135	790,547	16,878
50-54	2,978	695,927	20,725
55-59	3,923	695,927	27,301
60-64	4,700	567,023	26,650
65-69	5,874	567,022	33,307
Total of DALYs			145,405
DALYs (30-64)			112,098

(4,641 DALYs) / 1.6 = 2,901 DALYs

According to oecd, in 2017, the average annual wage in Greece was €17,336.[52]

Assuming that the average annual wage in 2018 remains on the same level as in 2017, we may estimate the gain of RMS technology in IHD patients in Greece:

(2,901 DALYs) X (17,336 € / year) = € 50,291,736 annually

As a result, the annual rate of DALYs in Greece in 30-69 aged of population is approximately 145,405. On regards of the workforce in Greece, DALYs are estimated to be nearly 112,100. The gain due to RMS use in the workforce of Greece is estimated as 386 PPYLL for the year 2050 and 2,901 DALYs per year, equal to € 50,291,736 annually.

In order to conclude, as IHD is a heavy burden for macro-economy of the country, more efficient innovative treatments should be considered.

Chapter 3

Direct Cost: Method and calculations

Before starting analyzing the method of the direct cost estimation we should clarify that the subgroups we name and the treatment are based on the ESC guidelines and market research. As we have already state, the patient's treatment is a decision made by the physicians and concern the patients individually. The current cost effectiveness analysis is an approach based on estimations and only the physicians are the ones who have the scientific background and experience to identify the number of devices per patient and medical treatment

3.1 Method

3.1.1 Cost Effectiveness of RMS in patient subgroups – Maximum Number of RMS per PCI

Initially we will estimate the post-procedure cost of DAPT in patients who had a prior-PCI and ACS afterwards due to stent thrombosis. As we have reported, RMS have demonstrated approximately zero scaffold thrombosis. We will compare the cost of re-hospitalization and revascularization due to stent thrombosis compared to RMS implantation during the first procedure.

Following the ESC guidelines, we assume that all patients having stent thrombosis are treated with p-PCI and no thrombolysis will be before. As it concerns DAPT, although the ESC guidelines recommend Prasugrel or Ticagrelor with an exception of Clopidogrel only when the previous are not available or are contraindicated, we will use really world data, which in the Greek market are as following: 60% of ACS patients treated either with Prasugrel or Ticagrelor and 40% treated with Clopidogrel. Since it is not identified the shares of Prasugrel and Ticagrelor in 60%, we assume that it is 30% each.

The costs that will be estimated will be:

- Post-revascularization DAPT cost, >12 months based on ESC guidelines, in MIs
- Cost of ambulance transportation
- Re-hospitalization and Revascularization cost based on DRG

Concerning the RMS that might had been implanted instead of 2nd generation DES during the 1st procedure, we assume that the cost –based on the National Tender- is €1,500/RMS unit. In addition, according to ESC guidelines, ST should be treated by a high pressure balloon dilation and Intra Vascular Ultra Sound (IVUS) catheter should be considered. We assume that approximately 20% of the cases are evaluated by IVUS, which means that the RMS unit price may be decreased by ~30€ which is the Non-Compliant Balloon (NCB) market price and 20% of 840€, which is the IVUS catheter cost. Because of the pre-mentioned the real burden due to RMS use would be ~1,302 €/unit. The rate of RMS units per patient is estimated as 1.6, based on Henry Dynant Real world All Comers registry.

We will compare the extra burden if during the 1st procedure an RMS be implanted instead to DES, with the cost of revascularization and re-DAPT treatment due to stent thrombosis. Moreover, we will estimate the maximum number of RMS that might be implanted in high thrombotic risk patients and in order RMS treatment be cost effective.

Additionally, since occasionally and based on individual evaluation of the patient needs and case characteristics, physicians suggest a prolonged DAPT in order to ensure absence of VLST, we will estimate the duration (in years), that RMS implantation may be cost effective compared to prolonged DAPT. We will assume an average interest rate 8% and based on this we will compare the DAPT cost in (n) years, the Net Present Value (NPV) of DAPT and compare it to RMS cost as above (1.6 RMS/patient, €1,500-140 = €1,360 per unit). With respect to NPV, we should consider the fact that even in RMS implantation case, DAPT treatment should be for one year (until the scaffold is fully absorbed, ESC guidelines). As for that, we will set as time zero point, the beginning of 2nd year after the procedure and estimate the time duration after which DAPT treatment is more costly compared to RMS implantation burden, based on the following:

$$\text{NPV} = \sum_{t=1}^{n} \frac{NCF_t}{(1+K)^t}$$

3.1.2 Investment does not always require budget

Based on the National Tender, scaffolds should initially -due to budget and early phase of the technology- share approximately 4.14% of all stents, which is equal to 1,025 units per year. The price should be maximum €1,500 per RMS unit, which requires €1,537,500 budget in total.[4]
Assuming that the mean rate of RMS is 1.6 RMS/patient, we will initially divide different budget amounts to RMS final price in order to find the number of RMS units and continuously the result will be divided to 1.6 in order to estimate the number of patients who may have the benefits of this technology.

We will create templates on regards of budget, RMS prices combined to payment terms and number of patients. Based on the templates we will create a relative graph.

3.2 Calculations

3.2.1 Cost Effectiveness of RMS in patient subgroups – Maximum Number of RMS per PCI

Aspirin = €1.17 per 20 units → 21.35 € / year
Prasugrel = €51.31 per 28 units → 668.86 € / year
Ticagrelor = €73.83 per 56 units, twice daily → 963.43 € / year
Clopidogrel = mean of (9.50 – 14.50) € = 12€ per 28 units → 156.43 € / year

DAPT cost = [(30%) x 668.86 + (30%) x 963.43 + (40%) x 156.43] + 21.35 = 573.61 € / year

RMS final price = [1,500 – 30 – (20% x 840] € / unit = 1,302 € / unit
Mean Rate of RMS = 1.6 RMS / patient
Total Burden due to RMS implantation per patient = 2,176 € / patient

Average Ambulance Transportation Cost [53] = 70 €
Re-hospitalization-Revascularization (MI due to Stent Thrombosis) [54] = 2,724 €
Retreatment of DAPT (12 months) = 573.61 €

Sum of Revascularization Costs = (70 + 2,724 + 573.61) € = 3,367.61 €

Result: Re-hospitalization and revascularization cost > Burden due to RMS implantation

Additionally, we will calculate the maximum allowed rate of RMS per patient:

3,367.61 / 1,302 = 2.6 RMS / patient

As a result, in high thrombotic risk patients, having increased possibility of potential ST based on physicians' evaluation, a rate of 1.6 RMS per patient is cost effective due to potential need of re-hospitalization and revascularization. Moreover, a rate < 2.6 RMS per patient remains cost effective in this subgroup of patients.

Concerning prolonged DAPT and in ACS patients, based on the pre-mentioned calculation:

DAPT cost = [(30%) x 668.86 + (30%) x 963.43 + (40%) x 156.43] + 21.35 = 573.61 € / year

and RMS real cost = (1,500 – 140)€ = 1,360€

RMS total cost = (1.6 RMS /patient) x 1,360€ = 2,176 € / patient

$$\text{NPV} = \sum_{t=1}^{n} \frac{NCF_t}{(1+K)^t} \quad \text{, (Equalization 1)}$$

Based on Equalization 1, in order NPV < 2,176€ , it should be t = 4 years and 8 months. Since we assumed that t = 0 at the end of 1^{st} year (both DES and RMS require 12months DAPT in ACS patients), we should add 1 year to the result.

According to the calculations, patients who have the need of prolonged DAPT , RMS implantation is cost effective as long as it concerns a need of DAPT for more than 5 years and 8 months, which is something to be consindered especially in young patients.

3.2.2 Investment does not always require budget

As pre-mentioned, we will estimate the number of patients who will have the benefit of RMS implantation based on several budgets depending on RMS unit price and terms on payments. For example and based on the National Tender:

Budget = 1,537,500€

RMS price unit = 1,500€

Budget / RMS unit price = 1,025 units

Mean rate of RMS / patient ~1.6

Number of patients = 1,025 / 1.6 = 641 patients

Table 3.1: RMS unit price = 2,000€, Payment Terms = 8 months (A)

Budget (€)	RMS Units	Nr of Patients
1,537,500	769	480
2,000,000	1,000	625
2,400,00	1,200	750
3,000,000	1,500	938

Table 3.2: RMS unit price = 1,500€ , Payment Terms = 3 months (B)

Budget (€)	RMS Units	Nr of Patients
1,537,500	1,025	641
2,000,000	1,333	833

2,400,00	1,600	1,000
3,000,000	2,000	1,250

Table 3.3: RMS unit price = 1,350€, Payment Terms = 30 days (C)

Budget (€)	**RMS Units**	**Nr of Patients**
1,537,500	1,139	712
2,000,000	1,481	926
2,400,00	1,778	1,111
3,000,000	2,222	1,389

Table 3.4: RMS unit price = 1,250€, Payment Terms = Cash (D)

Budget (€)	**RMS Units**	**Nr of Patients**
1,537,500	1,230	769
2,000,000	1,600	1,000
2,400,00	1,920	1,200
3,000,000	2,400	1,500

Although the National Tender claims that scaffold price should be < 1,500€/unit, the RMS market price in Greece is approximately 2,000€ due to two main reasons: a) the volume: the RMS suppliers offer the product at higher price since the orders concern 2-3 units and b) the payment terms: as the suppliers buy the product units and pay in cash and as the average payment terms are approximately 8 months, there is an extra cost which is included to the final unit price. Based on the Tables 3.1, 3.2, 3.3, 3.4 and diagram Figure 3.1, shorten of payment terms may allow RMS unit price decrease, (data from other EU countries), and even without any rise of budget, more patients may have the benefits of the innovative technology.

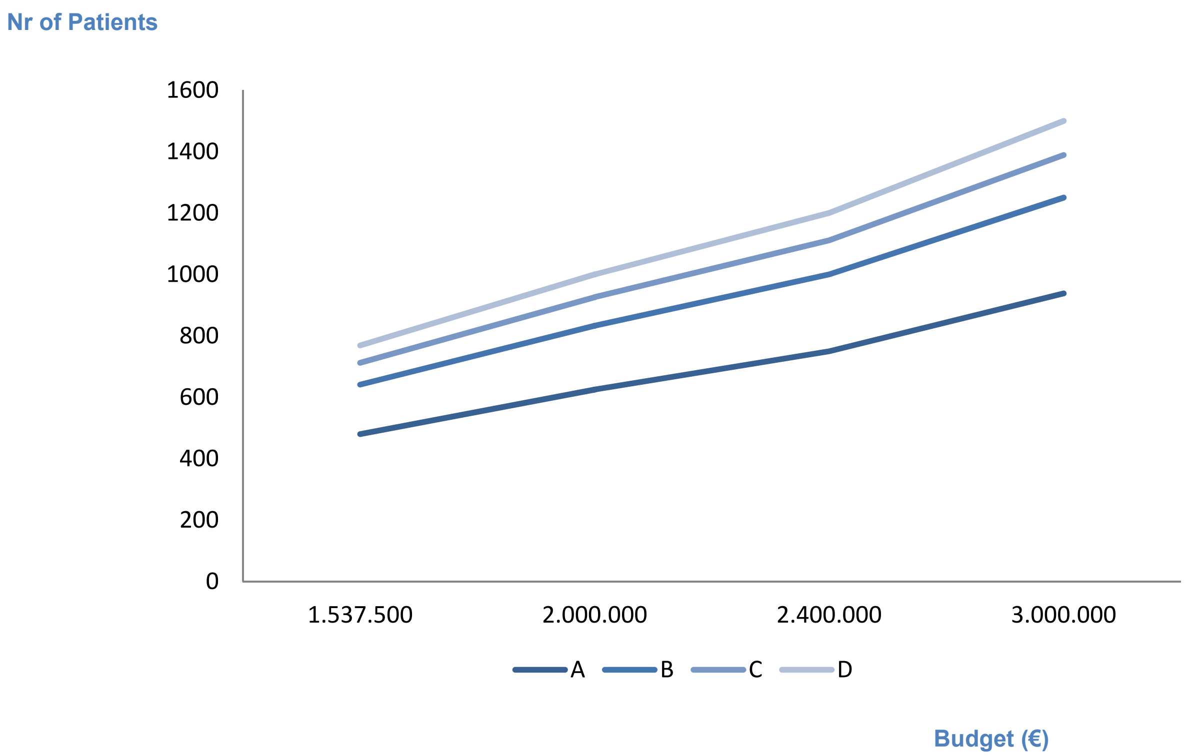


Figure 3.1: The diagram shows the relevance of budget, product price according to payment terms and the number of patients that might have the benefits of RMS technology.

Conclusion

Economic crisis in Greece has revealed several issues and healthcare system is not an exception. It should be our task to restructure, reorganize and do things on the right way. As Chilon the Lakedemoneios, one of the seven wise Ancient Greeks said: "*σπεῦδε βραδέως*" (hurry up slowly), we shouldn't let the healthcare expenditure decrease be a barrier for new technologies to offer their benefits to the patients. We should hurry up! Still, it should be done slowly, carefully…We should explore and evaluate alternative ways that combine cost effectiveness and social benefit.

Cost effectiveness and social benefit analysis is a tool to evaluate the benefits of new technologies. Coronary Artery Disease is quite costly and it is foreseen even more. It costs money and lives. Innovative products are supposed to be expensive. But are they? Compared to competition, yes, they are. Compared to quality of the patients lives, compared to the possibility of re-hospitalization and revascularization, compared to possibility of death due to late event? As CAD is claimed to be risen in workforce population of the country, the current cost effectiveness and social benefit analysis is an effort to explore if and under which conditions, groups of patient might have benefit of innovative technologies such as Resorbable Magnesium Scaffolds. We included several data based on publications, however, the patients that might be good candidates for RMS implantation and have the benefits of the technology, is and should be the physicians choice and individually to the patients. Because of that, we made our estimations based on the National Tender. All of the calculations were done according to the rate the Scientific Committee had suggested combining the need, the budget and the clinical data up to that time of period. We estimated both the indirect and direct cost, and we found out that in patients facing increased risk of thrombosis, RMS technology may be cost effective. Also, due to PPYLL and DALYs in workforce, macro- and micro-economy of the country may be enhanced.

Concerning the strategy approach that should be followed, since the market is price-sensitive, and since the pricing policy of the companies is payment terms-sensitive, we analyzed the affect to the number of patients due to payment terms shortening.. As we expected, the time duration of payment terms influences the product price and as a result the volume and the number of patients.

To summarize, the outcomes of this analysis are that Resorbable Magnesium scaffolds may be cost effective and socially beneficial and that an investment on “time” may be also efficient and fruitful, regardless budget investment. However, enriched clinical data and population statistics data would give us the opportunity to share a more enlightening analysis.

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