https://doi.org/10.31925/farmacia.2019.5.25 **ORIGINAL ARTICLE**

THE CARDIOVASCULAR MARKET IN ROMANIA DURING 1998 - 2017 PERIOD – ANALYSIS AND EVOLUTION

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Abstract

By all dimensions of analysis: units, DOT and values, the cardiovascular market has grown significantly over the last twenty years. However, it is still questionable if this development is enough, as cardiovascular diseases account for the most important mortality factor in Romania. Concerning therapeutic groups, of used cardiovascular drugs the biggest share in days of treatment belongs to C9 (inhibitors of the renin-angiotensin system), followed at certain distance by C10 (anti-atheroma agents and lipid regulators), C1 (cardiac therapy), C7 (beta-blocking agents), C8 (calcium antagonists) and C3 (diuretics). Regarding channels, retail channel accounts for dispensing almost all cardiovascular drugs. By administration route, oral solid forms are by far the most used form. Taking into consideration the product type, generic medicines are dominating in volume, while original medicines leads in value. Concerning market layers, volume and value of cardiovascular drugs are balanced between the 3 layers, while almost 2/3 of the population stays in the 3rd layer, which raises questions about the treatment accessibility in small cities and villages. Regarding INNs, there is a significant dynamic over the time; currently the most used are metoprolol, indapamide and atorvastatin.

Rezumat

Medicația cardiovasculară s-a dezvoltat susținut în ultimii douăzeci de ani în toate dimensiunile analizate: volum, zile de tratament, valoare. Pe grupe terapeutice, ca număr de zile de tratament, pe primul loc se situează inhibitorii sistemului renină-angiotensină (C9), urmați de agenți anti-aterom și regulatoare lipidice (C10), terapia cardiacă (C1), beta-blocante (C7), antagoniști de calciu (C8) și diuretice (C3). Pe canale, farmacia de retail eliberează medicația cardiovasculară aproape în totalitate. În ceea ce privește calea de administrare, există o majoritate covârșitoare pentru formele orale solide. Ca tip de produse, medicamentele generice ocupă cea mai mare parte ca volum, iar medicamentele originale ca valoare. Pe straturi, cele 3 straturi sunt comparabile ca volum și valoare, dar ținând cont că stratul 3 conține aproape două treimi din populație, ne putem întreba dacă accesibilitatea la tratament cardiovascular este bună la nivelul orașelor mici și al satelor. Ca DCI-uri, există o dinamică semnificativă de-a lungul timpului; cele mai folosite în momentul de față sunt metoprolol, indapamid și atorvastatină.

Keywords: ATC, cardiovascular medication, units, DOT, market layer, INN, administration route

Introduction

Cardiovascular diseases are one of the four major non-communicable diseases (NCDs), which are the leading causes of death worldwide, according to World Health Organization (WHO) report from 2018 [14]. In spite of decreases in mortality rates in many countries, cardiovascular diseases are responsible for 17.9 million deaths (representing 44% of all NCD deaths and 31% of global deaths) [3, 10, 14]. Consequently, they represent a global burden to the health-care system and one major cause of hospitalization and disabilitation among elderly and adults. For this reason, six medicines found on the 10 essential NCD medicines list are used for the secondary cardiovascular treatment: angiotensin-converting enzyme inhibitors, aspirin, beta-blockers, long-acting calcium channel blockers, statins, thiazide diuretics [13, 15]. Taking into account that cardiovascular diseases is one of the major mortality factor in Romania [1], the evolution of the cardiovascular drugs market has shown a sustained development for the last twenty years. The WHO country profile report has revealed that cardiovascular diseases are estimated to account for 56% of all deaths from Romania in 2016 [14].

Materials and Methods

We performed a retrospective study based on the information extracted from Pharma & Hospital Report (during a period of nineteen years, from 1998 to 2017) [11], a comprehensive pharmaceutical data issued monthly by Cegedim starting with 1996. Pharma & Hospital Report represents a statistical estimation of the medicines consumption at national level, using primary data from a panel of pharmacies.

Analysis has performed taking into account the following variables: Anatomical Therapeutic Chemical (ATC) groups (volume, DOT); channel; market layer; product type; administration route; International Non-proprietary Name (INN).

We have analysed the evolution of the cardiovascular market based on the ATC level 1 and 2 therapeutic groups over the period 1998 - 2017, separated in two decades, and compared the results obtained for 1998, 2007 and 2017 using as variables: volume, DOT and value. After that, we have carried out an analysis using units and values as variables in order to observe the differences between retail and hospital channel. Three market layers were defined and the penetration rate of cardiovascular drugs was established for 2007 and 2017. Furthermore, we have analysed the trends on the Romanian market taking into account the administration route and the product type (the distribution of original medicines compared with generic ones). In order to have a better perspective over the therapeutic developments and pharmaceutical evolution, the hierarchy of the most prescribed active substances was presented. As statins are being recommended as the first-line drugs for different cardiovascular diseases [6, 7], they have been analysed through product type, market layer and top INN.

Methodological specifications

ATC = Anatomical Therapeutic Chemical = 5-level classification system developed and updated yearly by the WHO Collaborating Centre for Drug Statistics Methodology; C = cardiovascular; Units = number of units (packs); DOT (Days of Treatment) = it was calculated based on the DDD (Defined Daily Dose), updated yearly by the WHO Collaborating Centre for Drug Statistics Methodology; MSP = Manufacturer Selling Price; MS = Market Share; Channel; Market layer; Product type = original (innovative) and generic medicines; Prescription drugs = Rx medicines (dispensed with a medical prescription); OTC drugs = OTC medicines (dispensed without a medical prescription); Administration route; INN = International Non-proprietary Name; RON = Lei; EUR = Euro; Millions.

Results and Discussion

Group C (cardiovascular) - total

As a total, the cardiovascular market has registered a significant growth (Table I), especially in the first decade (1998 - 2007): more than double in volume, more than quadruple in days of treatment and much more in value*. The next decade (2007 - 2017) shows also growth but rather in a stabilization pattern, as the market becomes more mature and offer and demand are closer than in the previous period.

Table I

ATC1 – Cardiovascular System

C (Cardiovascular System)	1998	2007	2007 *vs* 1998	2017	2017 *vs* 2007
Units (millions)	43.27	95.00	119.6%	135.63	42.8%
DOTs (millions)	431.40	1,721.20	299.0%	3,165.70	83.9%
MSP Value (mill. RON*)	37.38	1,088.20	2,811.2%	1,831.80	68.3%
DOT/unit	*9.97*	*18.12*	*81.7%*	*23.34*	*28.8%*
RON/unit	*0.86*	*11.45*	*1,226.0%*	*13.51*	*17.9%*
RON/DOT	*0.09*	*0.63*	*629.7%*	*0.58*	*-8.5%*

*The RON value in 1998 is somehow misleading, even it was made at the rate 10,000 ROL = 1 RON. The denomination (2005) does not contain long-time variation in value/purchasing power of the local currency

Also growth is displayed for the calculated averages: DOT/unit increase from 9.97 in 1998 to 23.34 in 2017 (change toward majority chronical treatment, 30 days a pack); RON/unit increase from 0.86 in 1998 to 13.51 in 2017 (we must remember that in 1998 the vast majority of cardiovascular consumption was made by domestic relatively old products, which additionally were at fix price in a period with very high devaluation/inflation); RON/DOT increase from 0.09 in 1998 to 0.58 in 2017 (with a notable exception of 8.5% decrease between 2007 - 2017, due to the administrative price reduction).

ATC2 therapeutic groups

The cardiovascular market based on the ATC level 2 [8, 18, 20] therapeutic groups shows the following trends in units (Table II): a significant growth for the groups C3 (diuretics), C7 (beta-blocking agents), C9 (inhibitors of the renin-angiotensin system) and C10 (anti-atheroma agents and lipid regulators); a moderate growth for the groups C4 (cerebral and peripheral vaso-therapeutics) and C5 (antivaricosis/antihaemorrhoidal preparations); a relative stagnation of C1 (cardiac therapy), C6 (other cardiovascular products) and C8 (calcium antagonists); a decrease of C2 (antihyper-tensives).

From the statistical point of view the sample sizes are relative small and in this working hypotheses we found that the assumptions of normality and sphericity doesn't check for applying the method of analysis of variance (ANOVA) with repeated measures. Thereby,

the p-values were calculated based on Friedman test, a non-parametric test, equivalent to repeated measures ANOVA. When it was necessary, we continued the statistical analysis with the Nemenyi post hoc test to compare all the pairs. For the statistical analysis of a cardiovascular system by ATC2 groups - units (Table II) we applied Friedmann test to find if there were significant differences between the studied years. We obtained a p-value = 0.009331 (< 0.05) which sustain the differences between time groups.

Table II

Cardiovascular by ATC2 groups - units

ATC1 ATC2	Units 1998 Millions	as % of total C	Units 2007 Millions	as % of total C	Units 2017 Millions	as % of total C
C (CARDIOVASCULAR SYSTEM)	**43.27**	**100.0%**	**95.00**	**100.0%**	**135.63**	**100.0%**
C1 (CARDIAC THERAPY)	10.72	24.8%	12.25	12.9%	12.36	9.1%
C2 (ANTIHYPERTENSIVES)	3.44	8.0%	0.65	0.7%	1.76	1.3%
C3 (DIURETICS)	2.17	5.0%	11.74	12.4%	17.16	12.7%
C4 (CEREBRAL AND PERIPHERAL VASOTHERAPY)	6.16	14.2%	11.29	11.9%	8.25	6.1%
C5 (ANTIVARICOSIS/ANTI-HAEMORRHOIDAL PREP)	5.52	12.8%	7.56	8.0%	9.93	7.3%
C6 (OTHER CARDIOVASCULAR PRODUCTS)	3.33	7.7%	2.57	2.7%	2.58	1.9%
C7 (BETA-BLOCKING AGENTS)	2.80	6.5%	13.25	13.9%	25.85	19.1%
C8 (CALCIUM ANTAGONISTS)	6.09	14.1%	5.67	6.0%	7.13	5.3%
C9 (AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM)	2.76	6.4%	23.09	24.3%	33.65	24.8%
C10 (LIPID-REGULATING/ANTI-ATHEROMA PREP)	0.28	0.6%	6.94	7.3%	16.54	12.2%
C11 (CARDIOVASCULAR MULTITHERAPY COMB PROD)	0.00	0.0%	0.00	0.0%	0.42	0.3%

In order to evaluate if each group are different from another one, we applied a post hoc test and we find a significative difference only between the group studied in 1998 and the one studied in 2017 with a p value = 0.011 (< 0.05). The other of p-values were not implying significant differences (Figures 1 and 2).

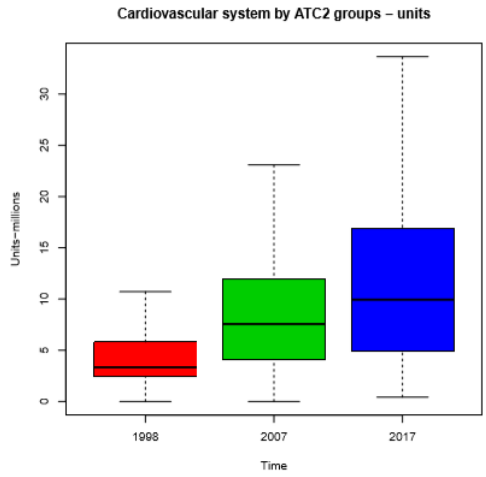

Figure 1.

Boxplot with three samples of every studied year for the comparison of millions of units of the cardiovascular market

Similar trends are registered in days of treatment (Table III), with the following exceptions: C1 (cardiac therapy) and C8 (calcium antagonists) have rather significant growth in DOTs compared with relative stagnation in units, as a result of consistent increase of DOT/unit.

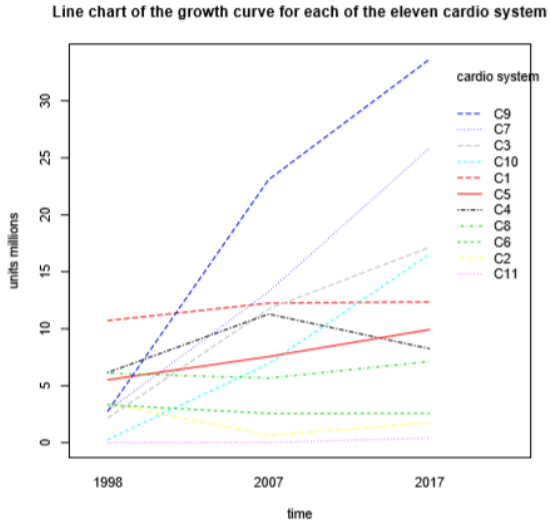

Figure 2.

A line chart of a cardio system displaying the increase and decrease of each therapeutic group

One of the initiatives of The European Society of Cardiology was the implementation of EUROSPIRE project, based on collecting data from hospital patients with coronary heart diseases. The EUROSPIRE IV survey, conducted in 24 European countries (2015 - 2016, Romania being one of them) showed that anti-platelets were the most used drugs (93.8%), followed by statins, with a large increase in prescribing (85.7%), then β-blockers (82.6%), and angiotensin-converting enzyme inhibitors (75.1%), observing a growth from the previous EUROSPIRE III survey results (91%; 80%; 78% and 71%, calcium channel blockers being mentioned as representing 25%). Consequently, it can be identified a significant growth,

similar with the situation showed in Table II for groups C7, C9 and C10, variations coming from differences between countries in national medical practice, lifestyles, risk factors for CVD [3, 4].

Table III

Cardiovascular by ATC2 groups - DOTs

ATC1 ATC2	DOT 1998 Millions	as % of total C	DOT 2007 Millions	as % of total C	DOT 2017 Millions	as % of total C
C (CARDIOVASCULAR SYSTEM)	**431.4**	**100.0%**	**1,721.2**	**100.0%**	**3,165.7**	**100.0%**
C1 (CARDIAC THERAPY)	121.3	28.1%	305.3	17.7%	370.5	11.7%
C2 (ANTIHYPERTENSIVES)	41.4	9.6%	15.3	0.9%	17.3	0.5%
C3 (DIURETICS)	55.3	12.8%	194.2	11.3%	267.8	8.5%
C4 (CEREBRAL AND PERIPHERAL VASOTHERAPEUTICS)	32.6	7.6%	107.6	6.3%	83.6	2.6%
C5 (ANTIVARICOSIS/ANTI-HAEMORRHOIDAL PREPARATIONS)	5.5	1.3%	7.6	0.4%	9.9	0.3%
C6 (OTHER CARDIOVASCULAR PRODUCTS)	3.3	0.8%	2.6	0.2%	2.6	0.1%
C7 (BETA-BLOCKING AGENTS)	33.4	7.7%	164.9	9.6%	370.9	11.7%
C8 (CALCIUM ANTAGONISTS)	87.2	20.2%	169.9	9.9%	300.4	9.5%
C9 (AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM)	47.1	10.9%	616.7	35.8%	1,303.6	41.2%
C10 (LIPID-REGULATING/ANTI-ATHEROMA PREPARATIONS)	4.3	1.0%	137.2	8.0%	438.7	13.9%
C11 (CARDIOVASCULAR MULTITHERAPY COMB PROD)	0.0	0.0%	0.0	0.0%	0.4	0.0%

Table IV

Cardiovascular by Channel

ATC1 CHANNEL	Units 1998 Mill.	as % of total C	Units 2007 Mill.	as % of total C	Units 2017 Mill.	as % of total C	Values 2007 Mill. RON	as % of total C	Values 2017 Mill. RON	as % of total C
C (CARDIO SYSTEM)	**43.3**	100.0%	**95.0**	100.0%	**135.6**	100.0%	**1,088.2**	100.0%	**1,831.8**	100.0%
Retail pharmacy	38.9	89.8%	93.0	97.9%	133.5	98.5%	1,069.4	98.3%	1,801.8	98.4%
Hospital pharmacy	4.4	10.2%	2.0	2.1%	2.1	1.5%	18.8	1.7%	30.0	1.6%

Channel

As shown in the Table IV, almost all (98.5% in 2017) of the cardiovascular diseases treatments are dispensed in the retail channel (ambulatory area) which means community pharmacies, while hospitals treats cardiovascular patients in acute status or with non-drug interventions. s.

Volume evolution reveals that an increased number of patients have been treated with cardiovascular medicines; while value analysis showed that this market has grown significantly (although maybe not enough, given the price reduction) in the last ten year. As the retail channel practically equals all chronic cardiovascular treatment and cardiovascular diseases as the first health problem in Romania, we believe that an increased importance is needed in the future, both in better treatment and in proper functioning of the retail channel.

Market layer

"Market layer" represents a purchasing behaviour attribute, derived from demographic criteria [16]; three "market layers" were defined: Bucharest and big cities (university cities or > 250,000 inhabitants); Medium cities (50,000 - 250,000 inhabitants); Small cities (< 50,000 inhabitants) and rural area. As this attribute was not available in 1998, we will see only last decade from this perspective (Table V).

Table V

Cardiovascular by Market layer

ATC1 MARKET LAYER	Popu-lation %	Units 2007 Mill.	as % of total C	Units 2017 Mill.	as % of total C	Values 2007 Mill.RON	as % of total C	Values 2017 Mill.RON	as % of total C
C (CARDIO SYSTEM)	**100.0%**	**95.0**	**100.0%**	**135.6**	**100.0%**	**1,088.2**	**100.0%**	**1,831.8**	**100.0%**
Important cities	19.3%	42.1	44.3%	48.2	35.5%	526.6	48.4%	696.1	38.0%
Medium-size cities	16.1%	24.0	25.3%	36.1	26.6%	270.2	24.8%	501.5	27.4%
Small cities & villages	64.6%	28.9	30.4%	51.3	37.8%	291.4	26.8%	634.2	34.6%

The penetration rate is significant in all three layers. However, although we assume that purchasing habits in important/medium-size cities include the treatment of certain patients from small cities and rural (parents, grandparents, other relatives), we can see a certain disbalance between important and medium-size cities,

on one hand, and small cities & villages, on the other hand. This disbalance is sizeable in both treatment volume (37.8% units *vs* 64.6% population in the 3rd layer) and value (34.6% value *vs* 37.8% volume in the 3rd layer, compared with 38.0% value *vs* 35.5% volume in the 1st layer).

Product type

According to patent ownership, original products (only branded) are the originators of the patent (Table VI), during and after protection, while generic medicines (branded or not) are marketed after the originators' patent protection have expired [17, 19].

Table VI

Cardiovascular by Product type

ATC1 STATUS PROD TYPE	Units 1998 Mill.	% as of total C	Units 2007 Mill.	% as of total C	Units 2017 Mill.	% as of total C	Values 2007 Mill. RON	% as of total C	Values 2017 Mill. RON	% as of total C
C (CARDIO SYSTEM)	**43.3**	**100.0%**	**95.0**	**100.0%**	**135.6**	**100.0%**	**1,088.2**	**100.0%**	**1,831.8**	**100.0%**
Rx drugs	***37.3***	***86.1%***	***88.4***	***93.1%***	***127.2***	***93.8%***	***1,041.3***	***95.7%***	***1,667.6***	***91.0%***
Original brands	2.8	6.5%	25.8	27.2%	49.1	36.2%	593.4	54.5%	988.5	54.0%
Branded generics	20.5	47.3%	43.0	45.3%	67.6	49.9%	378.2	34.8%	630.4	34.4%
Un-branded generics	14.0	32.3%	19.6	20.6%	10.5	7.7%	69.8	6.4%	48.8	2.7%
OTC drugs	***6.0***	***13.9%***	***6.6***	***6.9%***	***8.4***	***6.2%***	***46.9***	***4.3%***	***164.2***	***9.0%***

As cardiovascular drugs are mainly Rx, the table above displays that this market is dominated by generic medicines in volume, respectively by original medicines in value.

This was possible due to continuous increase of original drugs, in units the evolution was from 6.5% in 1998 to 27.2% in 2007 and 36.2% in 2017, while the generics have decreased accordingly; between generics, we may note the significant decrease of un-branded drugs (from 32.3% in 1998 to 20.6% in 2007 and 7.7% in 2017), while branded drugs share was relative constant.

Administration route

According to the administration route [9], there can be noticed changes in the way the treatment is administered in time (Table VII).

Table VII

Cardiovascular by Administration route

ATC1 ADMIN ROUTE	Units 1998 Millions	Units 2007 Millions	Units 2017 Millions	Values MSP 2007 RON Millions	Values MSP 2017 RON Millions
C (CARDIOVASCULAR SYSTEM)	**43.3**	**95.0**	**135.6**	**1,088.2**	**1,831.8**
infusion (i.v.)	0.1	0.1	0.1	2.2	17.6
inhalation	0.0	0.0	0.1	0.4	0.5
injectable	1.9	1.1	1.5	4.0	12.7
oral liquid	1.3	0.9	0.1	9.5	2.3
oral solid	35.7	88.9	129.9	1,051.8	1,730.7
rectal	2.2	1.4	1.2	3.8	16.2
topical	2.0	2.7	2.6	15.6	51.2
transdermal	0.0	0.0	0.1	0.8	0.7

From Table VII, oral solid pharmaceutical forms are exceeding by far other formulations, both in volume and value. Similar, for the statistical analysis of the cardiovascular system by administration route with ATC1 groups - units (Table VII) we applied the Friedmann test in order to find if there were significant differences between the studied years in relation with administration route. We obtained a p-value = 0.8574 (> 0.05) which revealed no differences between time groups (Figures 3 and 4).

Friedmann test was also applied for the statistical analysis of a cardiovascular system by administration route with MSP RON Millions values (Table VII) in order to find if there are significant differences between the studied years in relation with the administration route for financial cardiovascular market. We obtain p-value = 0.1573 (> 0.05), so we have no differences between time groups (Figures 5 and 6).

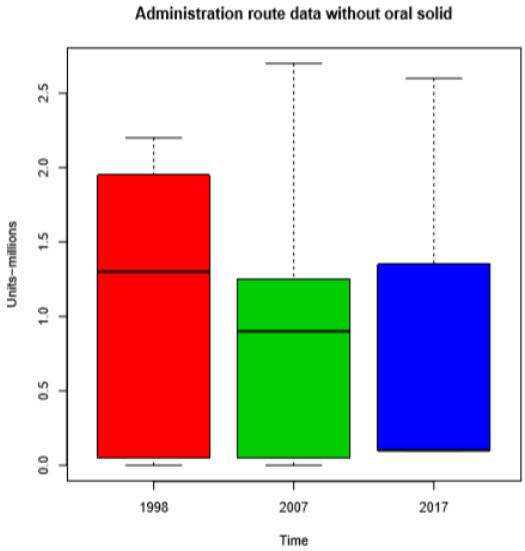

Figure 3.
Boxplot with three samples for every studied year for a comparation of units millions in relation to the administration route

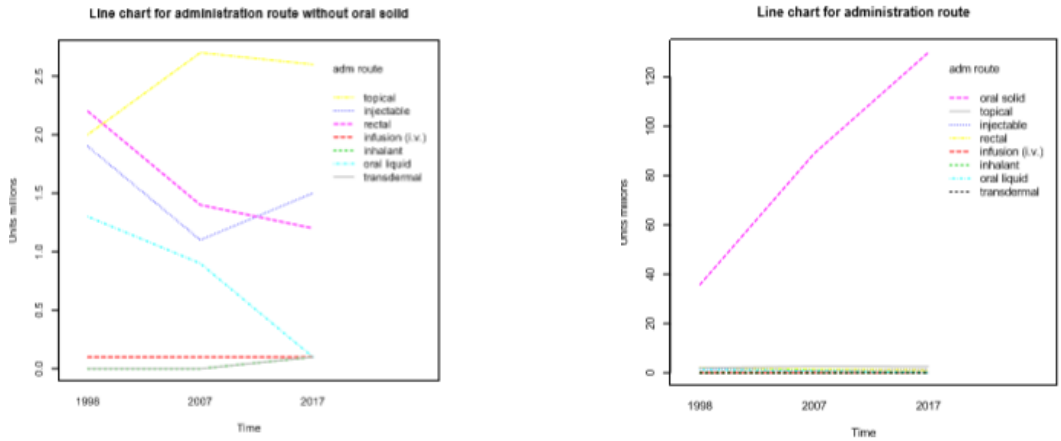

Figure 4.
A line chart of the cardiovascular market (units millions) which is displaying the increase and decrease for every administration route

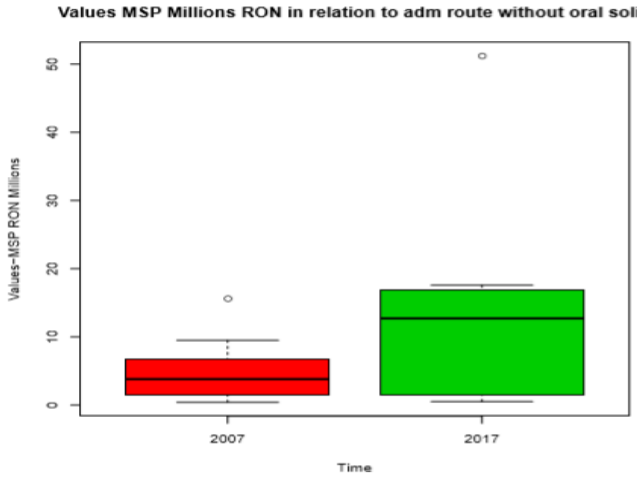

Figure 5.
Boxplot with two samples for every studied year for a comparation of financial market (millions RON) in relation with the administration route

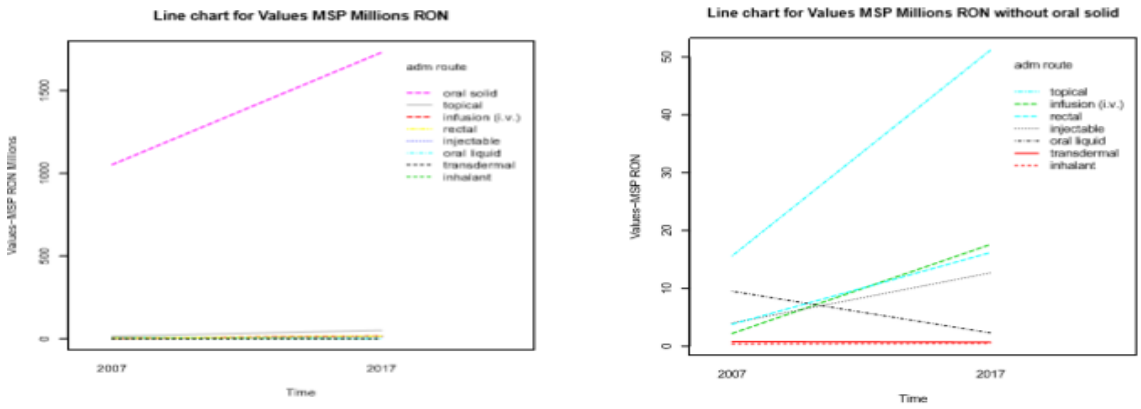

Figure 6.
A line chart of the financial cardiovascular market (millions RON) which is displaying the increase and decrease for every administration route

INNs

Regarding INNs [20], the performed analysis is rather difficult and question of relevance may arise; we have preferred a synthetic view (Table VIII) of the Top 10 INNs in 1998, 2007 and 2017, for the understanding of the therapeutic developments and pharmaceutical evolution.

We can notice that the first 3 INNs [20] in 2017 (*metoprololum*, *indapamidum* and *atorvastatinum*) had modest positions or did not exist in 1998. Also, the use of typical ACE inhibitors has declined: *captoprilum*, ranked 2nd in 1998 become 6th in 2007 and out of top 10 in 2017, while *enalaprilum*, ranked 3rd in 1998 become 1st in 2007 but ranks 4th in 2017.

Table VIII
Cardiovascular by Top 10 INNs

Rank	1998		2007		2017	
	INN	% volume	INN	% volume	INN	% volume
1	*acidum asparticum* K + Mg	7.7	*enalaprilum*	11.6	*metoprololum*	8.4
2	*captoprilum*	4.4	*metoprololum*	9.5	*indapamidum*	7.5
3	*enalaprilum*	1.9	*indapamidum*	7.7	*atorvastatinum*	5.4
4	*Ginkgo biloba*	0.7	*Ginkgo biloba*	5.1	*enalaprilum*	4.5
5	*nicergolinum*	0.5	*simvstatinum*	4.7	*perindorpilum* + *indapamidum*	3.5
6	*metoprololum*	0.5	*captoprilum*	4.1	*bisoprololum*	3.5
7	*trimetazidinum*	0.3	*trimetazidinum*	3.9	*nebivololum*	3.5
8	*indapamidum*	0.2	*acidum asparticum* K + Mg	2.7	*candesartanum*	3.2
9	*simvastatinum*	0.1	*diosminum* + *hesperidinum*	2.5	*diosminum* + *hesperidinum*	3.2
10	*diosminum* + *hesperidinum*	0.0	*nicergolinum*	2.5	*trimetazidinum*	3
	Total others	83.7	**Total others**	45.7	**Total others**	54.3

Example of details – Statins

Since their discovery and introduction into the clinical practice in the late 1980s, statins have proved to have a significant role in hyper-cholesterolemia management, in primary and secondary cardiovascular settings. European guidelines have shown that statins reduce the risk of cardiovascular events and mortality, having an important role in secondary prevention and being recommended as the first-line drugs for different cardiovascular diseases [6-8]. In Table IX we can see the marginal presence of statins in 1998, generics of statins in 2007 and the balance in 2017: generic statins [17, 19] account for two thirds in volume, almost three quarters in days of treatment and almost half in value.

Table IX
Statins by Product type

ATC4 PRODUCT TYPE	Units 1998 (000)	Units 2007 (000)	Units 2017 (000)	DOT 1998 (000)	DOT 2007 (000)	DOT 2017 (000)	Values 1998 000 RON	Values 2007 000 RON	Values 2017 000 RON
C10A1 (STATINS)	**36**	**5,441**	**13,336**	**449**	**110,254**	**388,062**	**952**	**155,088**	**212,392**
Original brands	36	970	3,526	449	25,232	101,615	952	58,491	111,231
Branded generics	0	4,346	9,809	0	82,759	286,446	0	92,642	101,160
Un-branded generics	0	125	0	0	2,262	1	0	3,956	1

The penetration rate in all three layers [16] is significant, but it is noticeably higher in the first layer, while in the last layer is clearly below average (Table X). Interesting to note that 2017 shares in all layers are pretty similar in units, days of treatment and value, which is not a very usual situation and shows that statin treatment is homogenous regardless the territorial dimension.

Table X

Statins by Market layer

ATC4 MARKET LAYER	Population	Units 2007	Units 2017	DOT 2007	DOT 2017	Values 2007	Values 2017
C10A1 (STATINS)	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**
Important cities	19.3%	51.1%	41.1%	51.9%	41.2%	52.8%	43.7%
Medium-size cities	16.1%	23.4%	25.4%	23.1%	25.2%	23.4%	26.0%
Small cities & villages	64.6%	25.5%	33.6%	24.9%	33.5%	23.8%	30.3%

Table XI

Statins - Top 5 INNs

Rank	1998		2007		2017	
	INN	% volume	INN	% volume	INN	% volume
1	*simvastatinum*	91.6	*simvastatinum*	81.9	*atorvastatinum*	54.72
2	*pravastatinum*	7.3	*atorvastatinum*	10.9	*rosuvastatinum*	27.72
3	*lovastatinum*	0.7	*rosuvastatinum*	4.7	*simvastatinum*	16.55
4	*fluvastatinum*	0.3	*fluvastatinum*	1.3	*pravastatinum*	0.44
5	*atorvastatinum*	0.1	*lovastatinum*	1.2	*lovastatinum*	0.43
	Total Others	**0.0**	**Total Others**	**0.0**	**Total Others**	**0.1**

It can be observed that the Top 5 INNs [20] are almost the same in two decades but their share has changed significantly due to a number of reasons, as therapeutic experience, price, availability etc. (Table XI).

From Table XI, the most commonly prescribed statin in the Romanian medical practice is *simvastatinum*, the only lipid-lowering agent mentioned on the current version of WHO Model List of Essential Medicines, since 2010 (the 21th list) [13, 15]. Until then, HMG-CoA reductase inhibitors were described as "*a family of potent and effective lipid-lowering drugs with a good tolerability profile"* but "*since no single drug has been shown to be significantly more effective or less expensive than others in the group, none is included in the Model List; the choice for of drug for use in patients at highest risk should be decided at the national level*"; therefore, no substance was present on the core list [12].

Conclusions

Taking into account all measures of analysis: units, DOT and values, the cardiovascular market has grown significantly over the last twenty years.

An increased number of patients has been treated for cardiovascular diseases which represents a positive development, judging the fact that the leading cause of death in Romania/a significant proportion of deaths and disability in Romania, as well as in other European countries, is represented/caused by cardio-vascular diseases.

The results of our study reveals that by therapeutic groups, the biggest share in days of treatment belongs to C9 (inhibitors of the renin-angiotensin system), followed at certain distance by C10 (anti-atheroma agents and lipid regulators), C1 (cardiac therapy), C7 (beta-blocking agents), C8 (calcium antagonists) and C3 (diuretics).

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