Electronic supplementary material

Adherence to guideline-directed medical therapy in patients with heart failure: a nationwide cohort study, 2014-2020.

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Abbreviations

HF:	heart failure
RASI:	renin-angiotensin system inhibitor
BB:	beta-blocker
MRA:	mineralocorticoid receptor antagonist
ACEI:	angiotensin-converting enzyme inhibitor
ARB:	angiotensin II receptor blocker
ARNI:	angiotensin receptor-neprilysin inhibitor
SGLT2:	sodium-glucose co-transporter 2
Dual HF therapy:	RASI + BB, RASI + MRA, or BB + MRA
Triple HF therapy:	RASI + BB + MRA
DDD:	defined daily dose
PDC:	proportion of days covered

ESM Table 1. Definitions

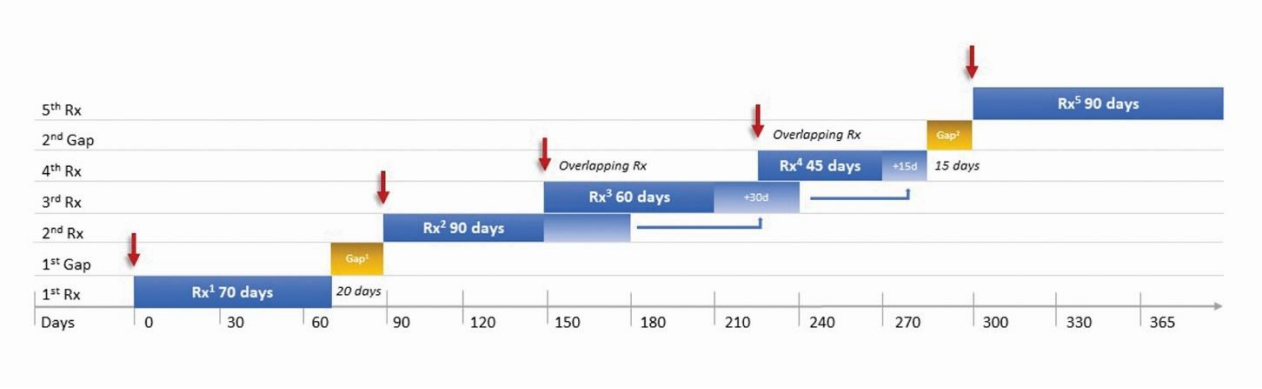
Condition	**NPR: ICD-10 code**	**NorPD: ATC code or reimbursement code (ICD-10 or ICPC-2)**
Heart Failure	I11.0, I13.0, I13.2, I42.x and I50.x	
Atrial fibrillation	I48	Reimbursement codes: I48, K78 (ICPC)
Cerebrovascular disease (including stroke and TIA)	G45, G46, H34.0, I60-I69	
Hypertension	I10, I11, I12, I13, I15	Reimbursement codes: I10-I13, I15 (ICD10) or K86, K87 (ICPC)
Ischemic heart disease	I20, I21, I22, I23, I24, I25	Reimbursement codes I20-I25 (ICD-10)
Myocardial infarction	I21, I22	
Peripheral artery disease	I70, I71, I72, I73, I74, I77, I78, I79, R02	
COPD	J40-J44	Reimbursement codes J40-J44 (ICD-10) or R95 (ICPC-2)
Anemia	D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64	ICPC: Reimbursement codes B80, B81, B82 or ICD10: D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64
Cancer	C00-C97	
Chronic kidney disease	N17-N19	
Dementia	F00, F01, F02, F03, G30, G31.8	Reimbursement code P70 (ICPC)
Depression	F32, F33	Reimbursement codes P03 (ICPC), P76 (ICPC) Or ATC-code N06A
Diabetes Mellitus	E10-E14	ATC codes: A10A or A10B or reimbursement codes: E10, E11, E13, E14 (ICD-10) or T89, T90 (ICPC-2)
Dyslipidemia	E78	Reimbursement codes: E78 (ICD-10) or T93 (ICPC) ATC-codes:C10A or C10B
Thyroid disease		ATC-codes: H03, H01AB or Reimbursement codes T85 (ICPC), T86 (ICPC)
Medication		**ATC-codes**
ACEI		C09AA01 captopril C09AA02 enalapril C09AA03 lisinopril C09AA04 perindopril C09AA05 ramipril C09BA01 captopril and diuretics C09BA02 enalapril and diuretics C09BA03 lisinopril and diuretics C09BA04 perindopril and diuretics C09BA05 ramipril and diuretics
ARB		C09CA01 losartan C09CA03 valsartan

		C09CA06 candesartan C09DA01 losartan and diuretics C09DA03 valsartan and diuretics C09DA06 candesartan and diuretics
ARNI		C09DX04 valsartan and sacubitril
BB		C07AB02 metoprolol C07AB07 bisoprolol C07AG02 carvedilol C07BB02 metoprolol and thiazides C07BB07 bisoprolol and thiazides
MRA		C03DA01 spironolactone C03DA04 eplerenone
Loop-diuretics		C03CA01 furosemide C03CA02 bumetanide
Co-medication		
High-ceiling diuretics		C03C
Antithrombotic agents		B01A, excluding B01AC
Calcium channel blockers		C08
Platelet aggregation inhibitors		B01AC
SGLT2 inhibitors		A10BK
Lipid-lowering therapy		C10A C10B

Comorbidities at baseline were based on registrations during the lookback period.
Medication at baselined were registered from -180 days to -1 days before index.

ESM Figure 1. Proportion of days covered

Schematic example of adherence to a single medication starting at the first prescription fill and with one year of follow-up. In this hypothetical example, the first fill lasts for 70 days, leaving a gap of 20 days until 2nd fill. As 3rd fill is overlapping with 30 days, the prescription is shifting (=stockpiling) by 30 days. The 4th fill is also overlapping with 15 days, leaving a gap of 15 days until the 5th fill. In this example, PDC equals the number of days covered (blue boxes) divided by days of observations = 330/365 = 0.9. PDC; proportion of days covered, Rx; prescription.



ESM Table 2. Guideline recommended treatment for heart failure and rationale for method

As for most claims databases worldwide, the NorPD does not contain information on the prescribed daily dose (PDD) by the treating physician. Some pharmacoepidemiologic studies use the 'defined daily dose' (DDD), defined by the World Health Organization (WHO) as the assumed average daily maintenance dose for a drug used for its main indication in adults. However, the DDD does not necessarily reflect the recommended or prescribed daily dose, and this is particularly evident for HF drugs as the main indication for most of these drugs are not HF but mild to moderate hypertension. This makes DDD a questionable surrogate for PDD. ESM Table 2 shows the uneven distribution of DDDs, both between and within drug groups, when DDD was calculated as a percentage of the target dose. Instead of using DDDs, we divided the dispensed quantity (number of pills) on the expected number of doses per day for each drug (the recommended daily regimen from the agent' product monograph or from clinical expert opinion) to calculate the duration of each dispensed prescription. We used one tablet a day for all drugs, except for Captopril, Carvedilol, Valsartan and Sacubitril/Valsartan (twice daily).

Medication	**No of tablets per day (products monograph)**	**Target dose/day**	**DDD (mg)**	**DDD as % of target dose**	**No of tablets per day (for PDC calculations)**
ACEI					
Captopril	2-3	150	50	0,33	2
Enalapril	2	20-40	10	0,25 - 0,5	1
Lisinopril	1	20-30	10	0,33 - 0,5	1
Ramipril	2	10	2.5	0,25	1
Perindopril	1	1.5-5	2.5	0,5 - 1,66	1
Beta-blocker					
Bisoprolol	1	10	10	1	1
Carvedilol	2	320	37.5	0,12	2
Metoprolol succinate	1	200	150	0,75	1
ARB					
Candesartan	1	32	8	0,25	1
Valsartan	2	320	80	0,25	2
Losartan	1	150	50	0,33	1
MRA					
Eplerenone	1	50	50	1	1
Spironolactone	1	50	75	1,5	1
ARNI					
Sacubitril/valsartan	2	97/103 b.i.d	2 tbl = 1 DDD	N/A	2

ESM Table 3 Baseline characteristics of the study population from 2014-2020

		2014	2015	2016	2017	2018	2019	2020
Patients (n)		7299	7482	7576	7931	8138	8474	7999
Age (median, IQR)		69 (60-75)	69 (60-75)	69 (60-75)	70 (60-75)	70 (60-75)	70 (60-75)	69 (59-75)
Age groups (%)								
	18-64	36 %	36 %	34 %	34 %	34 %	35 %	36 %
	65-80	64 %	64 %	66 %	66 %	66 %	65 %	64 %
Women age (median, IQR)		70 (62-76)	71 (62-76)	71 (63-76)	71 (63-76)	71 (63-76)	71 (62-76)	71 (60-76)
Men age (median, IQR)		68 (59-74)	68 (59-74)	68 (59-74)	69 (59-74)	68 (59-75)	69 (59-75)	69 (59-75)
Women, n (%)		36 %	36 %	36 %	36 %	38 %	38 %	38 %
ICD-codes for HF								
	I11,0	3,9 %	3,7 %	4,3 %	3,7 %	3,0 %	2,8 %	3,1 %
	I13,0	0,2 %	0,2 %	0,3 %	0,2 %	0,2 %	0,1 %	0,2 %
	I13,2	0,1 %	0,1 %	0,2 %	0,1 %	0,1 %	0,1 %	0,1 %
	I42,x	14,4 %	14,8 %	14,6 %	16,0 %	15,2 %	15,8 %	15,7 %
	I50,x	84,3 %	84,0 %	84,1 %	83,1 %	84,7 %	84,0 %	83,7 %
Comorbidities*								
	Atrial fibrillation	39 %	39 %	40 %	41 %	41 %	41 %	40 %
	Cerebrovascular event	12 %	14 %	13 %	15 %	15 %	15 %	15 %
	Hypertension	68 %	68 %	68 %	67 %	68 %	67 %	65 %
	IHD	50 %	48 %	48 %	47 %	48 %	48 %	46 %
	MI	26 %	26 %	26 %	26 %	26 %	26 %	25 %
	PAD	14 %	15 %	15 %	16 %	16 %	16 %	18 %
	COPD	22 %	23 %	23 %	24 %	25 %	26 %	23 %
	Anemi	15 %	17 %	18 %	18 %	19 %	20 %	20 %
	Cancer	17 %	18 %	20 %	21 %	22 %	23 %	25 %
	Chronic kidney disease	15 %	15 %	16 %	16 %	17 %	17 %	17 %
	Dementia	2 %	2 %	2 %	2 %	2 %	2 %	1 %
	Depression	26 %	28 %	29 %	28 %	30 %	29 %	31 %
	Diabetes Mellitus	22 %	23 %	22 %	22 %	23 %	24 %	23 %
	Dyslipidemia	56 %	56 %	57 %	56 %	58 %	58 %	56 %
	Thyroid disease	10 %	10 %	9 %	10 %	10 %	11 %	10 %
Patients on HF drugs before index**								
	ACEI	20 %	20 %	19 %	18 %	18 %	17 %	15 %
	ARB	20 %	21 %	21 %	22 %	23 %	21 %	22 %
	ARNI	0 %	0 %	0 %	0 %	0 %	0 %	0 %
	BB	44 %	43 %	42 %	42 %	42 %	42 %	39 %
	MRA	3 %	3 %	3 %	3 %	3 %	4 %	3 %
	Loop-diuretics	23 %	22 %	21 %	19 %	19 %	18 %	18 %
Other medication before index								
	Antithrombotic agents	24 %	25 %	26 %	28 %	28 %	27 %	28 %
	Platelet aggregation inhibitors	40 %	38 %	37 %	35 %	35 %	34 %	32 %
	Calcium channel blockers	22 %	20 %	21 %	21 %	20 %	20 %	20 %
	SGLT2	0 %	1 %	1 %	1 %	2 %	2 %	2 %

**Comorbidities: before index. **Medications: 180 to 1 days before index.*

ESM Table 4. Baseline characteristics of patients initiating ARNI

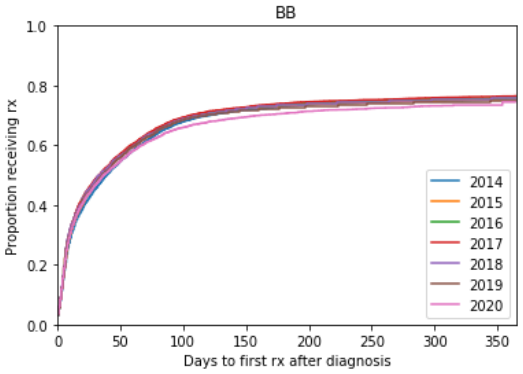
		Total	2016	2017	2018	2019	2020
New patients receiving ARNI each year (n)		2747	138	222	429	785	1173
Total patients receiving ARNI per year (n)			138	348	735	1463	2512
Age (median, IQR)		68 (58.0, 74.0)	65.5 (55.0, 73.0)	69.0 (59.3, 74.8)	68.0 (58.0, 74.0)	67.0 (57.0, 74.0)	69.0 (59.0, 75.0)
Age groups (%)							
	18-64 (%)	41 %	48 %	40 %	40 %	43 %	38 %
	65-80 (%)	59 %	52 %	60 %	60 %	57 %	62 %
Women, n (%)		19 %	17 %	15 %	23 %	17 %	21 %
Comorbidities* Cardiovascular							
	Atrial fibrillation	53 %	46 %	55 %	54 %	54 %	52 %
	Cerebrovascular event	14 %	9 %	16 %	13 %	13 %	16 %
	Hypertension	75 %	77 %	79 %	76 %	74 %	75 %
	Ischemic heart disease	71 %	78 %	76 %	71 %	69 %	71 %
	Myocardial infarction	34 %	37 %	31 %	34 %	34 %	35 %
	Peripheral arterial disease	17 %	14 %	20 %	15 %	18 %	17 %
Other							
	COPD	23 %	18 %	23 %	24 %	24 %	23 %
	Anemi	19 %	12 %	17 %	19 %	19 %	21 %
	Cancer	18 %	17 %	18 %	17 %	18 %	20 %
	Chronic kidney disease	22 %	25 %	22 %	25 %	21 %	20 %
	Dementia	1 %	1 %	1 %	0 %	1 %	0 %
	Depression	26 %	28 %	22 %	26 %	26 %	25 %
	Diabetes Mellitus	29 %	30 %	26 %	33 %	27 %	29 %
	Dyslipidemia	78 %	80 %	82 %	77 %	77 %	78 %
	Thyroid disease	9 %	8 %	7 %	7 %	9 %	10 %
Patients on HF drugs before index**							
	ACEI	60 %	68 %	64 %	68 %	63 %	54 %
	ARB	30 %	26 %	30 %	28 %	29 %	32 %
	BB	95 %	98 %	97 %	95 %	96 %	94 %
	MRA	59 %	67 %	68 %	62 %	63 %	52 %
	Loop-diuretics	64 %	78 %	69 %	67 %	64 %	59 %
Other medication before index							
	Anticoagulant agents	53 %	49 %	52 %	53 %	53 %	54 %
	Platelet aggregation inhibitors	56 %	68 %	56 %	58 %	55 %	55 %
	Calcium channel blockers	12 %	12 %	13 %	11 %	11 %	13 %
	SGLT2i	8 %	4 %	3 %	4 %	6 %	11 %

**Comorbidities: before index. **Medications: 180 to 0 days before index.*

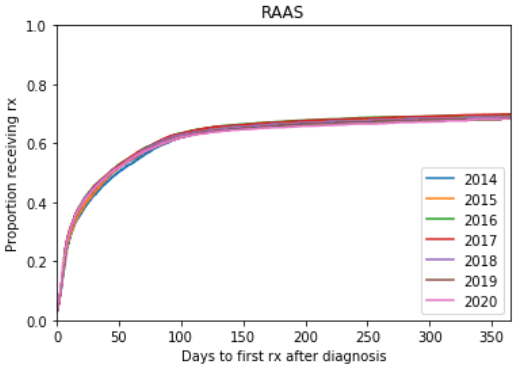
ESM Table 5. Drug initiation. Days from index HF to first prescription claim

	RASI	**BB**	**MRA**	**Any drug group**	**Dual HF therapy**	**Triple HF therapy**
Proportion of patients initiating drugs						
First prescription 0-30 days (n, %)	45%	47%	12%	62%	30%	7%
First prescription 0-60 days (n, %)	55%	59%	14%	74%	41%	9%
First prescription 0-90 days (n, %)	61%	67%	16%	80%	48%	11%
First prescription 0-365 days (n, %)	69%	75%	21%	87%	61%	16%

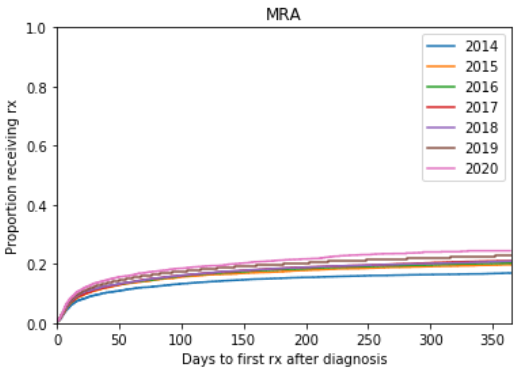
ESM Figure 2. Initiation per calendar year for (A) BB, (B) RASI, (C) MRA, and (D) ARNI



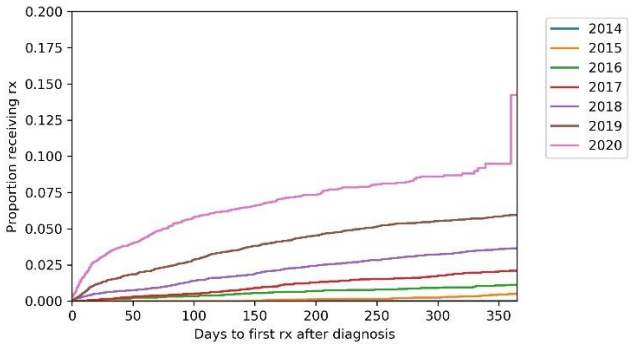
(A)



(B)



(C)

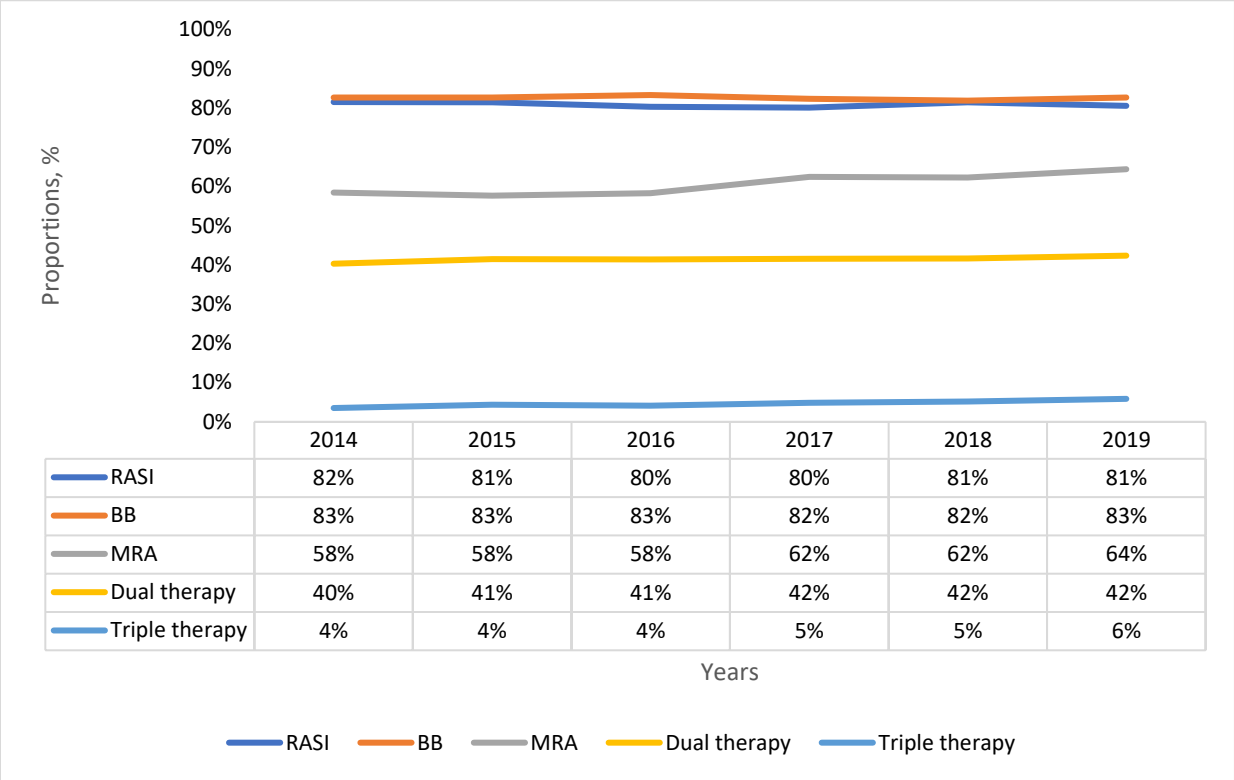


(D)

ESM Table 6: Adherence during the first year after initiation by 10% intervals in PDC

PDC	RASi	ARB	ACEI	ARNI	BB	MRA	At least 2 medications on the same day	Triple therapy
n	30,577	12,123	21,308	1,464	33,106	9,774	26,154	6,818
>0%	100 %	100 %	100 %	100 %	100 %	100 %	72 %	18 %
≥10%	100 %	99 %	100 %	98 %	99 %	100 %	70 %	17 %
≥20%	99 %	97 %	99 %	97 %	99 %	99 %	69 %	16 %
≥30%	95 %	90 %	93 %	95 %	96 %	87 %	65 %	13 %
≥40%	94 %	89 %	92 %	93 %	95 %	86 %	62 %	12 %
≥50%	93 %	86 %	91 %	92 %	93 %	84 %	59 %	11 %
≥60%	87 %	75 %	85 %	91 %	89 %	71 %	54 %	8 %
≥70%	84 %	71 %	83 %	88 %	87 %	67 %	49 %	7 %
≥80%	81 %	66 %	80 %	84 %	83 %	61 %	42 %	5 %
≥90%	73 %	57 %	73 %	76 %	74 %	49 %	32 %	3 %
Sensitivity analysis using prescription refill method								
PDC	RASi	ARB	ACEI	ARNI	BB	MRA	At least 2 medications on the same day	Triple therapy
>0%	100 %	100 %	100 %	100 %	100 %	100 %	69 %	18 %
≥10%	100 %	100 %	100 %	100 %	100 %	100 %	68 %	17 %
≥20%	100 %	100 %	100 %	100 %	100 %	100 %	67 %	16 %
≥30%	96 %	92 %	92 %	96 %	96 %	87 %	63 %	13 %
≥40%	95 %	92 %	91 %	96 %	96 %	87 %	61 %	12 %
≥50%	91 %	86 %	86 %	93 %	92 %	74 %	58 %	11 %
≥60%	90 %	84 %	84 %	92 %	90 %	71 %	54 %	9 %
≥70%	87 %	82 %	81 %	91 %	88 %	67 %	49 %	7 %
≥80%	80 %	73 %	74 %	88 %	80 %	55 %	42 %	5 %
≥90%	69 %	60 %	64 %	82 %	68 %	45 %	32 %	3 %

ESM Figure 3. Proportion of adherent patients (PDC ≥ 0.8) from 2014 to 2019



	2014	2015	2016	2017	2018	2019
RASI	82%	81%	80%	80%	81%	81%
BB	83%	83%	83%	82%	82%	83%
MRA	58%	58%	58%	62%	62%	64%
Dual therapy	40%	41%	41%	42%	42%	42%
Triple therapy	4%	4%	4%	5%	5%	6%

ESM table 7: Proportion of persistent patients with sensitivity analysis

Persistence (%)	**BB**	**RASI**	**MRA**
After 365 days			
Tablet method, 30 days grace period	71.8%	70.7%	47.8%
Tablet method, 90 days grace period	82.9%	81.8%	58.2
Prescription refill method, 30 days grace period	66.7%	67.3%	42.8%
Prescription refill method, 90 days grace period	81.7%	81.2%	55.8%
After 730 days			
Tablet method, 30 days grace period	58.3%	57.3%	31.3%
Tablet method, 90days grace period	73.3%	71.2%	41.3%
Prescription refill method, 30 days grace period	48.0%	48.3%	24.1%
Prescription refill method, 90 days grace period	70.6%	69.7%	39.7%
After 1825 days			
Tablet method, 30 days grace period	38,2 %	37,4 %	15,4 %
Tablet method, 90days grace period	56,8 %	52,7 %	24,0 %
Prescription refill method, 30 days grace period	24,1 %	22,4 %	9,0 %
Prescription refill method, 90 days grace period	51,1 %	49,1 %	21,9 %
After 2500 days			
Tablet method, 30 days grace period	31,0 %	30,5 %	11,4 %
Tablet method, 90days grace period	49,2 %	43,1 %	19,1 %
Prescription refill method, 30 days grace period	16,8 %	14,7 %	6,3 %
Prescription refill method, 90 days grace period	41,1 %	37,4 %	13,8 %