Supplemental material

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Supplemental Material

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Abbreviations: ATC, anatomical therapeutic chemical system; CI, confidence interval; cLQTS, congenital long QT syndrome; ICD-10, international classification of diseases system, 10th revision; ISCED, international standard classification of education; IQR, interquartile range; VT, ventricular tachycardia

Supplemental Table 1

Title: Baseline characteristics, patients with cLQTS attached to the workforce (cases) and patients with cLQTS not attached to the workforce (not included)

	cLQTS patients attached to the workforce (n=298)	cLQTS patients not attached to the workforce (n=44)	p-value
Sex (female)	192 (64.4)	29 (65.9)	0.98
Age at diagnosis, years (median (IQR))	38.6 [28.0, 47.9]	45.2 [39.8, 53.6]	0.0001
Social factors			
Education level			0.07
- Basic school <10 years (ISCED 0-2)	62 (22.3)	16 (36.4)	
- High school or vocational education (ISCED 3)	130 (46.8)	20 (45.5)	
- Higher education (ISCED 5-8)	86 (30.9)	8 (18.2)	
Living alone	103 (35.0)	17 (38.6)	0.77
Income			0.002
- 1. quartile (lowest)	75 (25.2)	5 (11.4)	
- 2. quartile	74 (24.8)	23 (52.3)	
- 3. quartile	74 (24.8)	8 (18.2)	
- 4. quartile (highest)	75 (25.2)	8 (18.2)	
Disease factors			
Disease manifestation			0.25
- Aborted cardiac arrest	26 (8.7)	6 (13.6)	
- VT or syncope	59 (19.8)	12 (27.3)	
- Unspecified	130 (43.6)	19 (43.2)	
- Asymptomatic	83 (27.9)	7 (15.9)	
Comorbidities prior to date of diagnosis			
Diabetes	12 (4.0)	≤3	1.00
Hypertension	31 (10.4)	14 (31.8)	0.0002
Ischemic heart disease or prior myocardial infarction	12 (4.0)	7 (15.9)	0.004
Atrial fibrillation	7 (2.3)	≤3	0.24
Epilepsy	4 (1.3)	≤3	1.00
Any psychiatric diagnosis	23 (7.7)	13 (29.5)	< 0.0001
Concomitant pharmacotherapy, <90 days prior to date of diagnosis			
Beta-blockers	89 (29.9)	20 (45.5)	0.06
Calcium antagonists	7 (2.3)	6 (13.6)	0.001
ACE inhibitors	12 (4.0)	6 (13.6)	0.02
Thiazides	6 (2.0)	≤3	0.61
Lipid lowering drugs	11 (3.7)	7 (15.9)	0.003
Antiepileptica	6 (2.0)	5 (11.4)	0.005
Antidepressants	14 (4.7)	9 (20.5)	0.0004
Anxiolytics	10 (3.4)	9 (20.5)	< 0.0001

Supplemental Table 2

Title: Baseline characteristics, patients with cLQTS stratified by disease manifestation

	Aborted cardiac arrest (n=27)	VT or syncope (n=58)	Unspecified (n=130)	Asymptomatic (n=83)	p-value
Sex (female)	18 (66.7)	45 (77.6)	82 (63.1)	47 (56.6)	0.08
Age at diagnosis, years (median (IQR))	39.6 [26.6, 50.1]	39.1 [25.3, 49.8]	36.6 [28.8, 47.9]	38.5 [27.9, 45.9]	0.89
Social factors					
Education level at diagnosis					0.60
- Basic school <10 years (ISCED 0-2)	6 (26.1)	13 (23.6)	31 (25.6)	12 (15.2)	
- High school or vocational education (ISCED 3)	12 (52.2)	26 (47.3)	51 (42.1)	41 (51.9)	
- Higher education (ISCED 5-8)	5 (21.7)	16 (29.1)	39 (32.2)	26 (32.9)	
Living alone	13 (48.1)	24 (42.1)	47 (37.0)	19 (22.9)	0.03
Employment status at baseline					0.90
- Employed	22 (81.5)	43 (74.1)	102 (78.5)	63 (75.9)	
- Study, maternity leave, vacation	≤3	9 (15.5)	18 (13.8)	14 (16.9)	
- Unemployed	≤3	6 (10.3)	10 (7.7)	6 (7.2)	
Income					0.59
- 1. quartile (lowest)	10 (37.0)	17 (29.3)	29 (22.3)	19 (22.9)	
- 2. quartile	6 (22.2)	15 (25.9)	35 (26.9)	18 (21.7)	
- 3. quartile	≤3	15 (25.9)	31 (23.8)	25 (30.1)	
- 4. quartile (highest)	8 (29.6)	11 (19.0)	35 (26.9)	21 (25.3)	
Comorbidities prior to date of diagnosis					
Diabetes	≤3	≤3	6 (4.6)	≤3	0.83
Hypertension	≤3	9 (15.5)	15 (11.5)	4 (4.8)	0.20
Ischemic heart disease or prior myocardial infarction	≤3	≤3	8 (6.2)	0	0.12
Atrial fibrillation	≤3	≤3	≤3	0	0.008
Epilepsy	≤3	0	≤3	≤3	0.58
Any psychiatric diagnosis	≤3	6 (10.3)	11 (8.5)	5 (6.0)	0.66
Concomitant pharmacotherapy, <90 days prior to date of diagnosis					
Beta blockers	5 (18.5)	18 (31.0)	47 (36.2)	19 (22.9)	0.11
Calcium antagonists	0	≤3	4 (3.1)	≤3	0.63
ACE inhibitors	≤3	5 (8.6)	4 (3.1)	≤3	0.26
Thiazides	0	≤3	≤3	≤3	0.27
Lipid lowering drugs	≤3	≤3	7 (5.4)	≤3	0.56
Antiepileptica	≤3	≤3	≤3	0	0.004
Antidepressants	≤3	≤3	8 (6.2)	≤3	0.64
Anxiolytics	≤3	≤3	≤3	≤3	0.61

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Supplemental Table 3

Title: *Findings in the patients with cLQTS with additional clinical information available*

	Patients with cLQTS (n=156)
Sex (female)	105 (67.3)
Age at diagnosis, years	38.3 [25.3, 46.9]
Proband	65 (41.7)
Relative	91 (58.3)
Genetics	
KCNQ1	41 (26.3)
KCNH2	75 (48.1)
SCN5A	11 (7.1)
Genonegative	18 (11.5)
Not tested	8 (5.1)
Disease manifestation	
ACA	20 (12.8)
VT/syncope	44 (28.2)
Unspecified	9 (5.8)
Asymptomatic	82 (53.2)

Supplemental Table 4

Title: Baseline characteristics, patients with cLQTS attached to the workforce and patients with cLQTS not attached to the workforce or dead six months after diagnosis

	Attached to the workforce (n=271)	Not attached to the workforce or dead (n=27)	p-value
Sex (female)	174 (65.2)	18 (66.6)	0.97
Age at diagnosis, years (median [IQR])	38.2 [28.0, 47.8]	40.5 [28.8, 49.5]	0.63
Social factors			
Education level			
- Basic school <10 years (ISCED 0-2)	56 (22.0)	6 (25.0)	
- High school or vocational education (ISCED 3)	120 (47.2)	10 (41.7)	
- Higher education (ISCED 5-8)	78 (30.7)	8 (33.3)	0.87
Living alone	94 (35.2)	9 (33.3)	1
Employment status 30 days prior to date of diagnosis			
- Employed	208 (76.8)	22 (81.5)	
- Study, maternity leave, vacation	42 (15.5)	≤3	
- Unemployed	21 (7.7)	4 (14.8)	0.14
Income			
- 1. quartile (lowest)	66 (24.4)	9 (33.3)	
- 2. quartile	67 (24.7)	7 (25.9)	
- 3. quartile	69 (25.5)	5 (18.5)	
- 4. quartile (highest)	69 (25.5)	6 (22.2)	0.71
Disease factors			
Disease manifestation			
- Aborted cardiac arrest	17 (6.3)	10 (37.0)	
- VT or syncope	49 (18.1)	9 (33.3)	
- Unspecified	125 (46.1)	5 (18.5)	
- Asymptomatic	80 (29.5)	≤3	<0.0001
Comorbidities prior to date of diagnosis			
Diabetes	9 (3.3)	≤3	0.15
Hypertension	28 (10.3)	≤3	1
Ischemic heart disease or prior myocardial infarction	10 (3.7)	≤3	0.67
Atrial fibrillation	6 (2.2)	≤3	1
Epilepsy	≤3	≤3	0.81
Any psychiatric diagnosis	21 (7.7)	≤3	1
Concomitant pharmacotherapy, <90 days prior to date of diagnosis			
Beta blockers	80 (29.5)	9 (33.3)	0.85
Calcium antagonists	7 (2.6)	0	0.86
ACE inhibitors	10 (3.7)	≤3	0.67
Tiazides	5 (1.8)	≤3	1

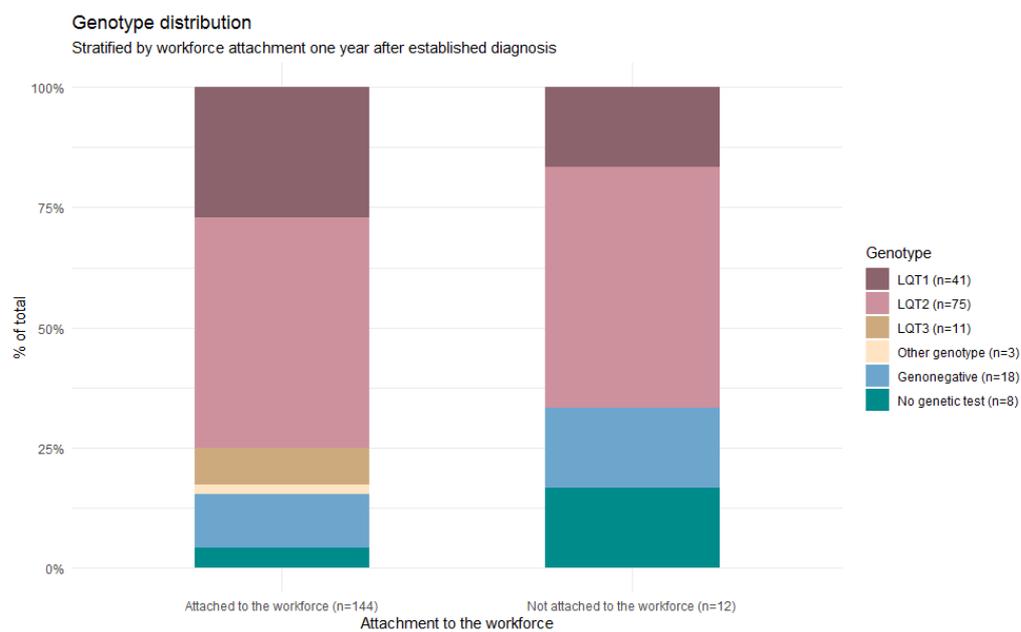|			
Lipid lowering agents	11 (4.1)	0	0.60
Antiepileptics	4 (1.5)	≤3	0.17
Anxiolytics	8 (3.0)	≤3	0.51
Antidepressants	13 (4.8)	≤3	1

Supplemental Table 5

Title: Baseline characteristics, patients with cLQTS attached to the workforce and patients with cLQTS not attached to the workforce or dead one year after diagnosis

	Attached to the workforce (n=278)	Not attached to the workforce or dead (n=20)	p-value
Sex (female)	182 (65.5)	10 (50.0)	0.25
Age at diagnosis, years (median [IQR])	37.5 [27.9, 47.8]	44.5 [33.2, 50.4]	0.13
Social factors			
Education level at diagnosis			
- Basic school <10 years (ISCED 0-2)	59 (22.5)	≤3	
- High school or vocational education (ISCED 3)	123 (46.9)	7 (43.8)	
- Higher education (ISCED 5-8)	80 (30.5)	6 (37.5)	0.83
Living alone	95 (34.7)	8 (40.0)	0.81
Employment status 30 days prior to date of diagnosis			
- Employed	213 (76.6)	17 (85.0)	
- Study, maternity leave, vacation	43 (15.5)	0	
- Unemployed	22 (7.9)	≤3	0.11
Income			
- 1. quartile (lowest)	70 (25.2)	5 (25.0)	
- 2. quartile	66 (23.7)	8 (40.0)	
- 3. quartile	71 (25.5)	≤3	
- 4. quartile (highest)	71 (25.5)	4 (20.0)	0.38
Disease factors			
Disease manifestation			
- Aborted cardiac arrest	22 (7.9)	5 (25.0)	
- VT or syncope	51 (18.3)	7 (35.0)	
- Unspecified	123 (44.2)	7 (35.0)	
- Asymptomatic	82 (29.5)	≤3	0.005
Comorbidities prior to date of diagnosis			
Diabetes	10 (3.6)	≤3	0.41
Hypertension	28 (10.1)	≤3	0.75
Ischemic heart disease or prior myocardial infarction	11 (4.0)	≤3	1
Atrial fibrillation	6 (2.2)	≤3	0.96
Epilepsy	4 (1.4)	0	1
Any psychiatric diagnosis	21 (7.6)	≤3	1
Concomitant pharmacotherapy, <90 days prior to date of diagnosis			
Beta blockers	81 (29.1)	8 (40.0)	0.44
Calcium antagonists	7 (2.5)	0	1

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ACE inhibitors	10 (3.6)	≤3	0.41
Tiazides	5 (1.8)	≤3	0.87
Lipid lowering agents	11 (4.0)	0	0.77
Antiepileptics	5 (1.8)	≤3	0.87
Anxiolytics	8 (2.9)	≤3	0.29
Antidepressants	12 (4.3)	≤3	0.54

Supplemental Figure 1

Title: cLQTS disease manifestation according to genotype

Disease manifestation by genotype
At time of LQTS diagnosis
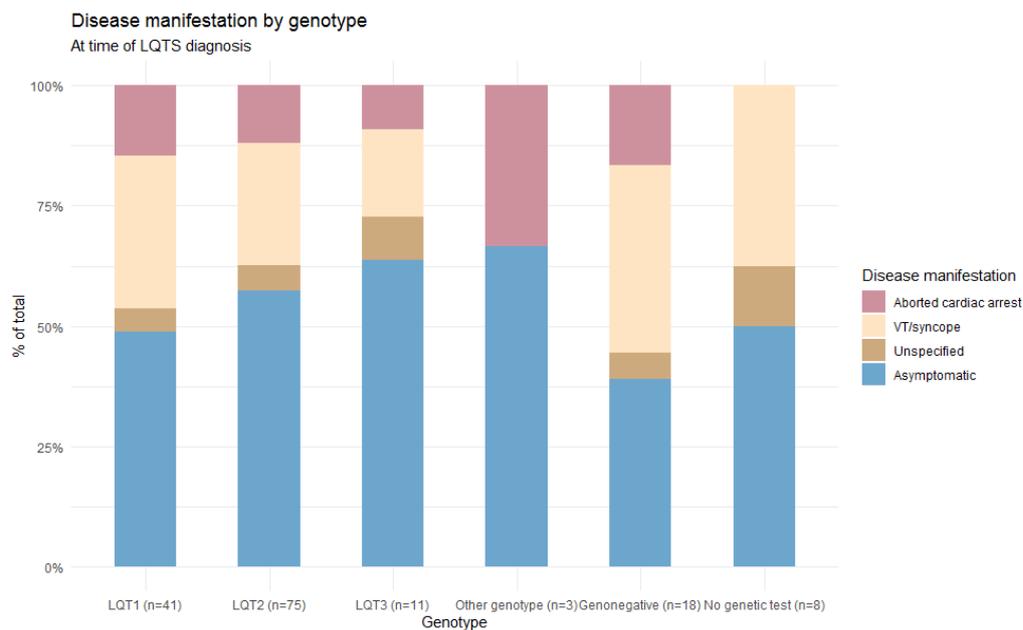
Supplemental Figure 2

Title: Workforce attachment according to genotype

Attachment to the workforce
One year after established diagnosis

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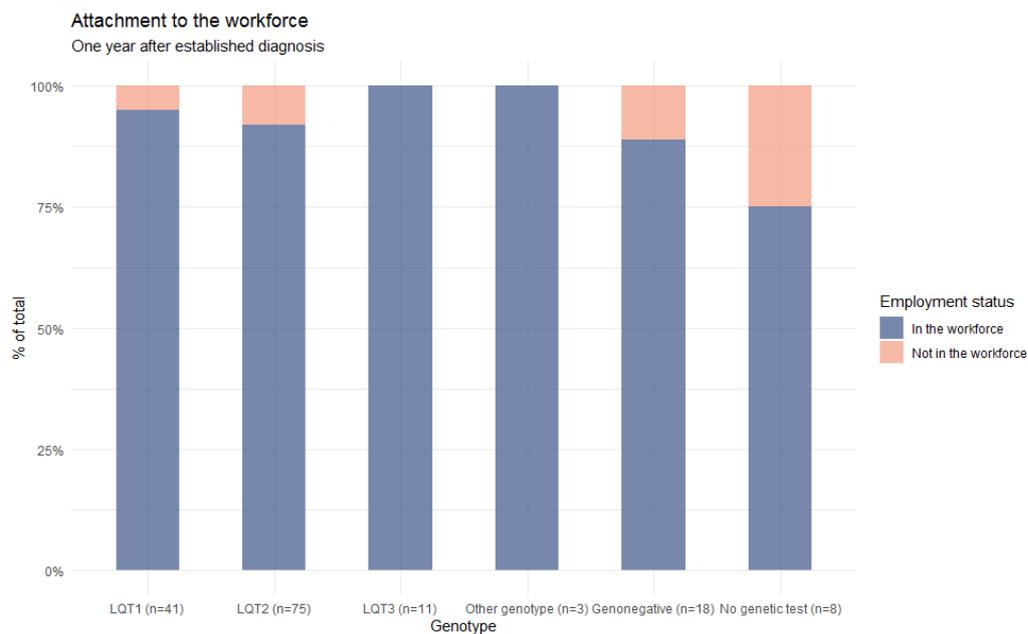
Supplemental Figure 3

Title: Genotype distribution according to workforce attachment

Genotype distribution
Stratified by workforce attachment one year after established diagnosis

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Supplemental Figure 4

Title: *Odds ratio of detachment from the workforce among patients with cLQTS, six months after diagnosis*
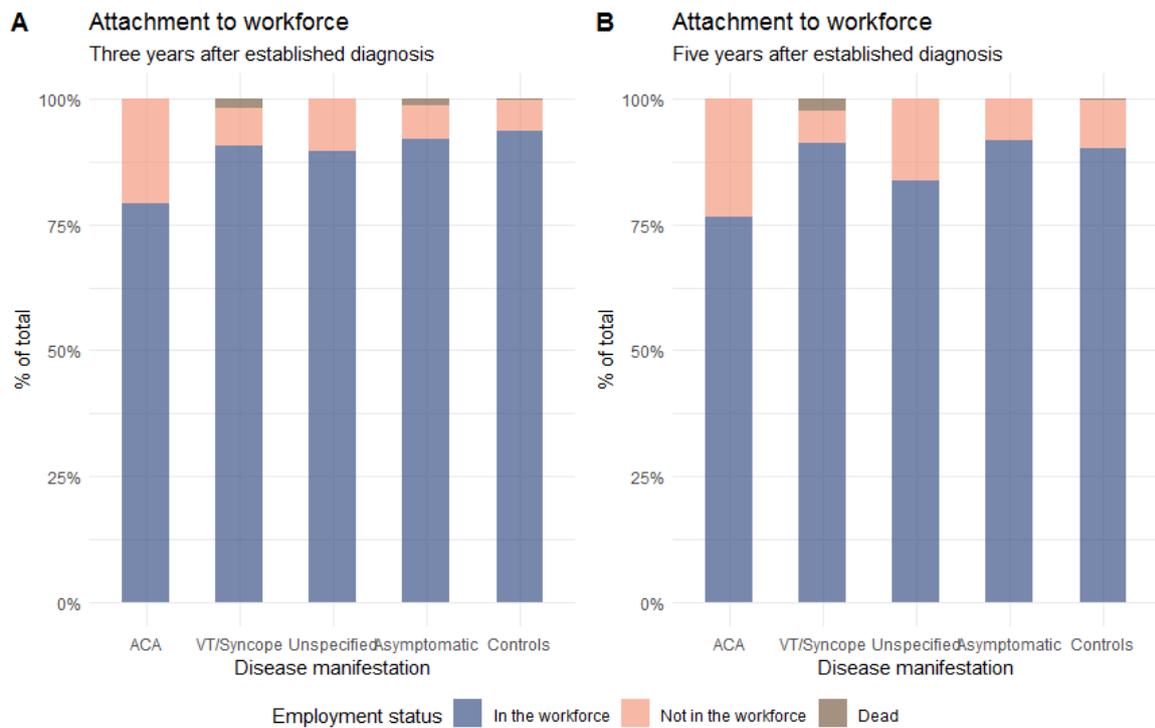
Legend: Forest plot showing odds ratio of detachment from the workforce for different risk factors within the group of cLQTS patients six months after diagnosis with cLQTS.

Risk factors	Odds Ratio [95% CI]
Age at diagnosis	
Age 18-30	Reference
Age 30-45	1.70 (0.32 - 9.00)
Age 45-60	1.16 (0.19 - 7.07)
Sex	
Female	1.69 (0.55 - 5.16)
Disease manifestation	
Asymptomatic	Reference
Unspecified	0.74 (0.15 - 3.61)
VT or syncope	5.01 (1.16 - 21.66)
Aborted cardiac arrest	23.79 (4.74 - 119.46)
Comorbidities at diagnosis	
Hypertension	0.68 (0.14 - 3.22)
Diabetes	6.61 (1.05 - 41.48)
Any psychiatric diagnosis	1.02 (0.19 - 5.55)
Employment status at diagnosis	
Employed	Reference
Study/maternity leave, vacation, etc.	0.26 (0.03 - 2.55)
Unemployed	2.31 (0.44 - 12.16)
Education level at diagnosis	
Basic school	Reference
High school or Vocational education	0.75 (0.20 - 2.89)
Higher education	1.38 (0.29 - 6.55)
Indexregulated income	
1. quartile	Reference
2. quartile	1.38 (0.26 - 7.42)
3. quartile	0.90 (0.13 - 6.12)
4. quartile	0.67 (0.09 - 5.11)
Living alone	0.55 (0.17 - 1.75)

Odds Ratio (95% CI)

Supplemental Figure 5

Title: Workforce attachment after cLQTS diagnosis according to disease manifestation and age-, sex-, and employment status-matched controls

Legend: Bar chart showing proportion of patients with cLQTS (stratified by disease manifestation) and matched control population attached to the workforce (A)three years and (B)five years after time of diagnosis (index date for control population); ACA, aborted cardiac arrest; VT, ventricular tachycardia

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Supplemental Appendix

Codes for treatment and diagnosis definition

Diagnoses/comorbidities	ICD codes
Aborted cardiac arrest	I469, I460, I490, I490B
Anoxic brain damage	G931
Any psychiatric disease	F
Atrial fibrillation	I48
Epilepsy	G40, G41
Ischemic heart disease or prior myocardial infarction	I20-25
Syncope	R559
Ventricular tachycardia	I470, I472, I472A, I472B, I472D

Therapy	ATC codes
ACE-inhibitors	C09A
Antiarrhythmic drugs	C01B
Antidepressants	N06A
Anxiolytics	N05B, N05C
β blockers	C07
Calcium channel blockers	C08
Lipid lowering drugs	C10
Loop diuretics	C03C
Thiazides	C03A

Comorbidities based (partly) on ATC codes	ATC or ICD codes
Diabetes[1]	Diagnosis code within 5 years of diagnosis of ICD10: E10-E14 *and/or* A dispensed prescription within 180 days of diagnosis of the following: ATC: A10
Hypertension[2]	2 or more dispensed prescriptions of the following within 180 days of diagnosis (ATC): α adrenergic blockers: C02A, C02B, C02C Non-loop diuretics: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52 Vasodilators: C02DB, C02DD, C02DG β blockers: C07 Calcium channel blockers: C07F, C08, C09BB, C09DB Renin–angiotensin system inhibitors: C09

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