Supplementary text

Left ventricular ejection fraction was calculated by Simpson's biplane method [1]. LV restrictive filling pattern was defined according to current guidelines [2]. Left atrium end systolic-diameter was measured in the parasternal long-axis view. Mitral regurgitation was assessed using a multiparametric approach and was categorized in mild vs moderate-severe [3].

With the use of next-generation sequencing (NGS), the genetic testing covered more than 95% of known DCM-related genes, as previously reported [4]. The variants were all validated with bidirectional Sanger sequencing and were therefore classified according to current guidelines [5]. The minor allele frequency was verified in the gnomAD database (https://gnomad.broadinstitute.org/variant/22-46449891-G-A) and crosschecked with the ClinVar (http://www.ncbi.nlm.nih.gov/clinvar) and Cardio Classifier (https://www.cardioclassifier.org) databases. Rare variants in genes with similar functions or part of the same cellular compartment were clustered in different groups, as previously described [6].

References

1) Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015 Jan;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.
2) Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the

European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016 Apr;29(4):277-314.

3) Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30(4):303-371. doi:10.1016/j.echo.2017.01.007.
4) Gigli M, Merlo M, Graw SL, Barbati G, Rowland TJ, Slavov DB et al. Genetic Risk of Arrhythmic Phenotypes in Patients With Dilated Cardiomyopathy. J Am Coll Cardiol. 2019 Sep 17;74(11):1480-1490. doi: 10.1016/j.jacc.2019.06.072.
5) Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. 2018 May;24(5):281-302. doi: 10.1016/j.cardfail.2018.03.004. Epub 2018 Mar 19.
6) Dal Ferro M, Stolfo D, Altinier A, Gigli M, Perrieri M, Ramani F et al. Association between mutation status and left ventricular reverse remodelling in dilated cardiomyopathy. Heart. 2017 Nov;103(21):1704-1710. doi: 10.1136/heartjnl-2016-311017. Epub 2017 Apr 17.

Supplementary Table S1. Furosemide, bisoprolol and Ramipril conversions .

Furosemide dose equivalent	Torasemide	Bumetanide					
	X 4	X 40					
Bisoprolol dose equivalent	Carvedilol	Metoprolol	Atenolol				
	/ 5	/ 20	/ 10				
Ramipril dose equivalent	Enalapril	Lisinopril	Captopril	Candesartan	Valsartan	Losartan	Sacubitril/valsartan
	/ 2	/3.5	/ 15	/ 3.2	/ 32	/ 15	24/26 mg = 2.5 49/51 mg = 5 mg 97/103 mg = 10 mg

Supplementary Table S2. Characteristics of the total starting population divided according to the baseline diuretic dose.

1131 patients	N	Total population (1131, 100%)	No LDs (393, 35%)	FED daily dose 1-40 mg (508, 45%)	FED daily dose 40-80 mg (171, 15%)	FED daily dose >80 mg (59, 5%)	p-value
Age, years	1131	50 (40-60)	44 (34-56)	53 (43-62)	54 (43-63)	51 (44-60)	0.349
Male sex, no. (%)	1131	788 (70)	277 (71)	337 (66)	123 (72)	51 (86)	**<0.001**
Disease duration, months	806	6 (1-27)	9 (2-39)	5 (1-23)	4 (1-25)	20 (2-80)	0.103
Enrollment decade 1990-2000 200-2010 2010-2019	1131	 363 (32) 411 (36) 357 (32)	 137 (35) 129 (33) 127 (32)	 159 (31) 211 (42) 138 (27)	 50 (29) 54 (32) 67 (39)	 17 (29) 17 (29) 25 (42)	0.008
Heart rate, bpm	1085	74 (17)	69 (13)	76 (18)	79 (20)	80 (16)	0.062
AF	1033	117 (11)	20 (6)	58 (12)	29 (18)	10 (20)	**<0.001**
SBP, mmHg	888	120 (110-140)	120 (110-140)	120 (110-140)	120 (110-140)	120 (110-130)	**0.047**
NYHA III or IV, no. %	1072	235 (22)	0 (0)	132 (27)	74 (47)	30 (55)	**<0.001**
LBBB, no. %	1114	343 (31)	105 (27)	167 (34)	50 (30)	21 (36)	0.163
TTNtv	301	55 (18)	18 (15)	6 (12)	29 (25)	2 (18)	0.360
Genetic negative/other variant	301	246 (82)	106 (86)	45 (88)	86 (75)	9 (82)	0.097
Creatinine, mmol/l	914	89 (80-106)	88 (76-97)	90 (80-106)	95 (80-107)	97 (88-107)	0.038
Hb, g/dl	852	14.1 (13.0-15.0)	14.2 (13.3-15.2)	14.1-13.2-14.9)	13.9 (14.8-12.8)	14.2-12.9-14.8)	0.229
Sodium, mEq/l	684	140 (138-142)	141 (139-142)	140 (138-142)	140 (138-142)	138 (137-140)	**0.001**
LVEF, %	1131	32 (25-39)	38 (32-44)	29 (24-35)	28 (22-33)	24 (20-30)	**<0.001**
LVEDVI, ml/m^2	1131	87 (70-111)	77 (64-96)	89 (74-114)	97 (81-123)	105 (89-126)	**0.001**
LAESD, mm	1042	41 (35-47)	37 (32-42)	42 (36-47)	45 (40-50)	51 (42-55)	**<0.001**
Moderate or severe MR, no. (%)	1072	385 (34)	56 (15)	209 (43)	84 (52)	36 (66)	**<0.001**
RFP, no. (%)	895	205 (18)	33 (10)	100 (25)	55 (43)	17 (46)	**<0.001**
ACE-I or ARB or ARNI, no. (%)	1131	1091 (97)	362 (92)	505 (99)	166 (97)	58 (98)	**<0.001**
Ramipril dose equivalent, mg	1118	5.0 (2.5-10.0)	4.3 (2.5-7.5)	5 (2.9-10)	5 (2.5-10)	5 (2.5-10)	0.765
Beta-blockers, no. (%)	1131	1011 (89)	336 (86)	463 (91)	158 (92)	54 (92)	0.020
Bisoprolol dose equivalent, mg	980	2.50 (1.25-5.0)	2.5 (1.25-5)	2.5 (1.9-5)	2.5 (1.25-5)	3.6 (1.25-5)	0.696
MRA, no. (%)	1131	486 (43)	39 (10)	270 (53)	127 (74)	50 (85)	**<0.001**
Ivabradine, no. %	1131	38 (3)	5 (1)	18 (4)	8 (5)	7 (12)	**<0.001**
Diuretics, no. (%)	1131	738 (65)	0 (0)	508 (100)	171 (100)	59 (100)	-
Furosemide dose equivalent, mg	1131	25.0 (0-25.0)	0 (0-0)	25 (12.5-25.0)	50 (50-50)	100 (100-125)	**<0.001**
CRT, no. %	1131	140 (12)	30 (8)	69 (14)	27 (16)	14 (24)	**0.001**
ICD, no. %	1131	304 (27)	90 (23)	144 (28)	53 (31)	17 (29)	0.277

AF, atrial fibrillation; SBP, systolic blood pressure; NYHA, New York Heart Association; LBBB, left bundle branch clock; LVEF, left ventricular ejection fractionLVEDVI, left ventricular end-

diastolic volume index; LAESD, left atrial end-systolic diameter; IVS: interventricular septum; MR mitral regurgitation; RFP, restrictive filling pattern; ACE-i, angiotensin-converting enzyme–inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineralocorticoid receptors antagonists; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator. In bold are reported variables with significant differences amongst groups. Shadowed rows show variables with p value <0.001.

Supplementary Table S3. Univariate and multivariable analysis for dose↓ diuretics trajectory. Only patients with available information regarding diuretic trajectory were included (follow-up population).

	Univariate, HR (95% C.I.), p value	Multivariable, HR (95% C.I.), p value
Clinical evaluation		
Age, per year	0.992 (0.986-0.998), p=0.005	0.999 (0.992-1.007), p=0.876
BMI per Kg/m^2	0.960 (0.941-0.980), p<0.001	**0.968 (0.941-0.995), p=0.022**
Male sex	1.064 (0.882-1.282), p=0.518	
Disease duration per month	1.000 (0.997-1.002), p=0.723	
Enrollment decade (compared to 1990-2000) 2000-2010 2010-2020	 1.109 (0.904-1.361), p=0.320 1.213 (0.984-1.496), p=0.070	
Heart rate per bpm	0.998 (0.993-1.003), p=0.393	
AF	0.916 (0.678-1.238), p=0.569	
SBP per mmHg	1.001 (0.997-1.006), p=0.583	
NYHA III or IV	0.729 (0.583-0.911), p=0.005	0.997 (0.735-1.354), p=0.986
LBBB	0.717 (0.591-0.870), p=0.001	0.794 (0.615-1.024), p=0.076
Creatinine per mg/dl	1.001 (0.991-1.031), p=0.608	
Sodium per mEq/l	0.995 (0.966-1.026), p=0.764	
Echocardiography		
LVEF per %	1.026 (1.017-1.036), p<0.001	**1.021 (1.006-1.036), p=0.006**
LVEDD per mm	0.972 (0.962-0.981), p<0.001	0.989 (0.974-1.004), p=0.989
LAESD per mm	0.980 (0.969-0.990), p<0.001	0.999 (0.982-1.016), p=0.900
Moderate or severe MR	0.720 (0.596-0.870), p=0.001	0.923 (0.705-1.208), p=0.559
RFP	0.721 (0.556-0.919), p=0.008	0.861 (0.641-1.155), p=0.318
Medications and device therapy		
ACE-i/ARB/ARNI	0.730 (0.492-1.083), p=0.118	
Ramipril/ARNI dose equivalent per mg	0.975 (0.958-0.992), p=0.005	0.986 (0.965-1.008), p=0.214
Beta-blockers	1.009 (0.754-1.350), p=0.953	
Bisoprolol dose equivalent per mg	0.990 (0.964-1.016), p=0.444	
MRA	0.794 (0.666-0.948), p=0.011	0.959 (0.743-1.239), p=0.750
Ivabradine	0.899 (0.480-1.685), p=0.741	
Furosemide dose equivalent per 20 mg	0.970 (0.947-0.980), p<0.001	1.001 (0.996-1.007), p=0.689
CRT	1.535 (0.569-4.137), p=0.397	
ICD	1.283 (0.764-2.153), p=0.346	

BMI, body mass index; AF, atrial fibrillation; SBP, systolic blood pressure; NYHA, New York Heart Association; LBBB, left bundle branch clock; Hb, hemoglobin; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LAESD, left atrial end-systolic diameter; MR mitral regurgitation; RFP, restrictive filling pattern; ACE-i, angiotensin-converting enzyme–inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineralocorticoid receptors antagonists; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator. In bold are reported variables with significant association at multivariable analysis

Supplementary Table S4. Comparison between patients withdrawing loop diuretics and patients not withdrawing loop diuretics.

608 patients	N	Loop diuretics withdrawal (143, 24%)	No loop diuretics withdrawal (465, 76%)	p-value
Age, years	608	48 (41-58)	55 (46-64)	**<0.001**
Male sex, no. (%)	608	95 (66)	48 (34)	0.313
Disease duration, months	576	3 (1-12)	6 (1-29)	**0.007**
Enrollment decade 1990-2000 200-2010 2010-2019	608	 59 (41) 46 (32) 38 (27)	 136 (29) 170 (37) 159 (34)	**0.024**
Heart rate, bpm	595	76 (66-90)	75 (64-88)	0.204
AF	558	10 (8)	70 (16)	**0.009**
SBP, mmHg	595	123 (115-140)	120 (110-140)	0.858
NYHA III or IV, no. %	570	36 (27)	162 (37)	**0.034**
LBBB, no. %	599	38 (27)	164 (36)	**0.031**
TTNtv	162	13 (33)	22 (18)	**0.047**
Creatinine, mmol/l	535	90 (80-106)	93 (80-106)	0.553
Hb, g/dl	494	14.2 (13.2-15.1)	14.0 (13.0-14.9)	0.969
Sodium, mEq/l	395	140 (138-142)	140 (138-142)	0.900
LVEF, %	608	29 (23-37)	28 (22-33)	0.281
LVEDVI, ml/m^2	608	88 (74-119)	93 (80-106)	0.517
LAESD, mm	568	42 (37-47)	43 (38-49)	0.068
Moderate or severe MR, no. (%)	584	55 (40)	226 (51)	**0.013**
RFP, no. (%)	456	28 (23)	123 (37)	**0.004**
ACE-I or ARB or ARNI, no. (%)	608	143 (100)	461 (99)	0.341
Ramipril dose equivalent, mg	604	5.0 (2.5-10.0)	5.0 (2.5-10.0)	0.048
Beta-blockers, no. (%)	608	137 (96)	426 (92)	0.062
Bisoprolol dose equivalent, mg	511	3.75 (2.5-7.5)	2.5 (1.25-5.0)	**0.021**
MRA, no. (%)	608	75 (52)	309 (67)	**0.002**
Ivabradine, no. %	608	5 (4)	23 (5)	0.321
Furosemide dose equivalent, mg	608	25.0 (12.5-25.0)	25.0 (25.0-50.0)	**0.001**
CRT, no. %	608	13 (9)	85 (18)	**0.005**
ICD, no. %	608	41 (28)	152 (33)	0.213

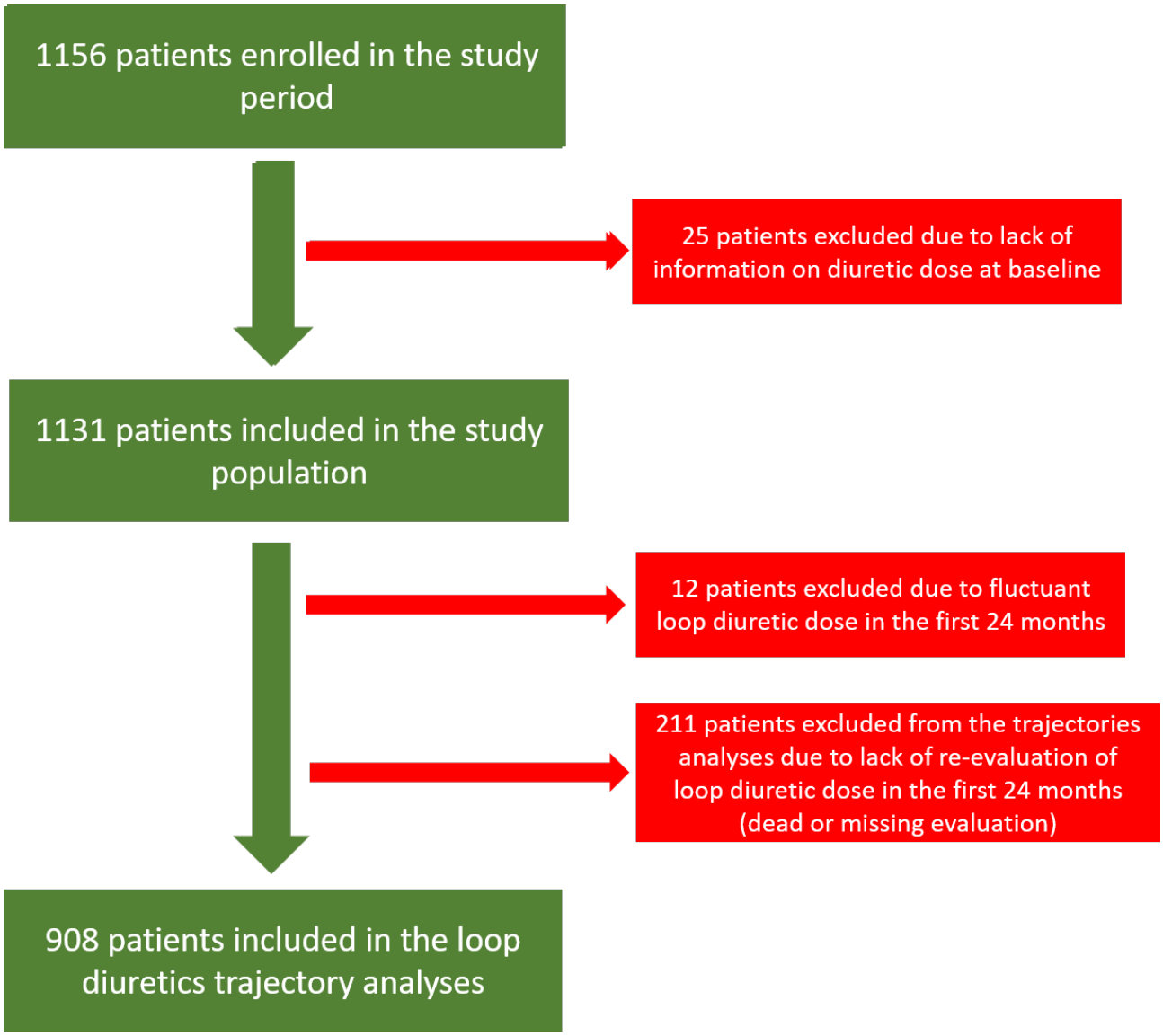
BMI, body mass index; AF, atrial fibrillation; SBP, systolic blood pressure; NYHA, New York Heart Association; LBBB, left bundle branch clock; TTNtv: Titin truncating variant; Hb, hemoglobin; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; IVS, interventricular septum; LAESD, left atrial end-systolic diameter; MR mitral regurgitation; RFP, restrictive filling pattern; ACE-i, angiotensin-converting enzyme–inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineralocorticoid receptors antagonists; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator. In bold are reported variables with significant differences amongst groups.

Supplementary Table S5. Uni- and multivariable analysis for diuretic withdrawal within 24 months. Only patients taking diuretics at baseline with a second assessment within 24 months are included.

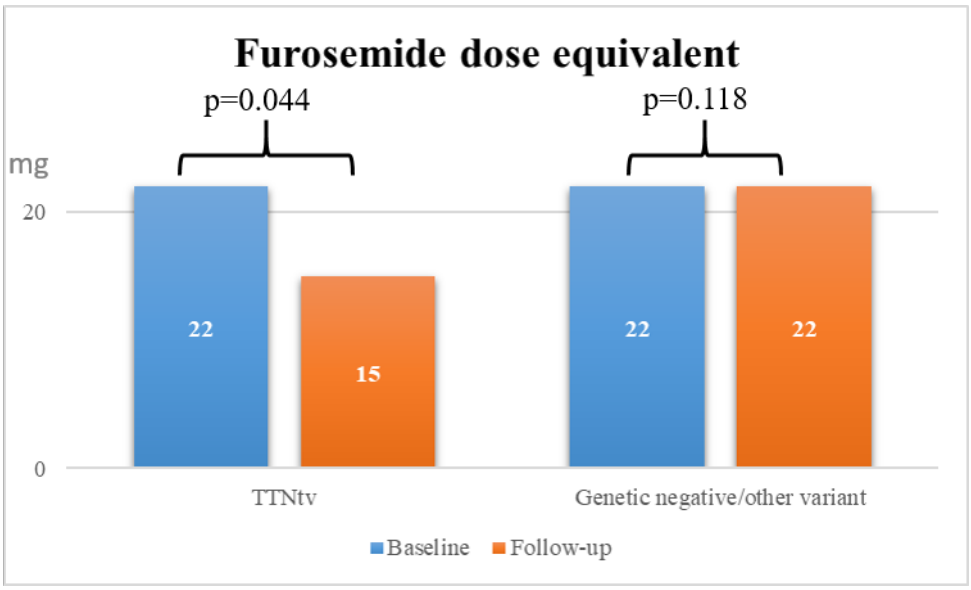
	Univariate, HR (95% C.I.), p value	Multivariable, HR (95% C.I.), p value
Clinical evaluation		
Age, per year	0.978 (0.967-0.989), p<0.001	**0.976 (0.954-0.997), p=0.029**
BMI per Kg/m^2	0.951 (0.917-0.986), p=0.007	0.957 (0.893-1.025), p=0.211
Male sex	0.899 (0.636-1.272), p=0.549	
Disease duration per month	0.991 (0.985-0.997), p=0.004	0.995 (0.986-1.004), p=0.283
Enrollment decade (compared to 1990-2000) 2000-2010 2010-2020	Reference 1.695 (1.127-2.548), p=0.011 1.109 (0.722-1.705), p=0.636	Reference 1.276 (0.561-2.900), p=0.561
Heart rate per bpm	1.007 (0.998-1.016), p=0.118	0.589 (0.244-1.425), p=0.240
AF	0.916 (0.678-1.238), p=0.569	
SBP per mmHg	1.010 (1.002-1.018), p=0.015	
NYHA III or IV	0.677 (0.461-0.995), p=0.047	0.572 (0.264-1.242), p=0.158
LBBB	0.695 (0.479-1.008), p=0.055	
QRS duration per msec	0.990 (0.984-0.996), p=0.002	0.994 (0.985-1.003), p=0.213
Creatinine per mmol/l	0.990 (0.565-1.449), p=0.677	
Sodium per mEq/l	1.033 (0.974-1.097), p=0.276	
Echocardiography		
LVEF per %	1.022 (1.003-1.041), p=0.025	0.982 (0.943-1.002), p=0.369
LVEDD per mm	0.982 (0.964-1.001), p=0.062	
IVS per mm	0.974 (0.910-1.042), p=0.437	
LAESD per mm	0.975 (0.955-0.995), p=0.013	1.027 (0.977-1.079), p=0.298
Moderate or severe MR	0.663 (0.472-0.931), p=0.018	**0.454 (0.219-0.939), p=0.033**
RFP	0.557 (0.365-0.850), p=0.007	0.914 (0.418-2.000), p=0.823
Medications and device therapy		
ACE/ARB/ARNI	-	
Ramipril dose equivalent per mg	0.998 (0.966-1.031), p=0.891	
Beta-blockers	1.958 (0.865-4.435), p=0.107	
Bisoprolol dose equivalent per mg	1.063 (1.018-1.110), p=0.005	**1.092 (1.027-1.161), p=0.005**
MRA	0.597 (0.430-0.829),=0.002	0.905 (0.487-1.683), p=0.753
Ivabradine	0.680 (0.279-1.661), p=0.398	
Furosemide dose equivalent per 20 mg	0.741 (0.633-0.867), p<0.001	0.787 (0.598-1.035), p=0.112
CRT	0.561 (0.079-4.012), p=0.565	
ICD	0.692 (0.221-2.173), p=0.529	

BMI, body mass index; AF, atrial fibrillation; SBP, systolic blood pressure; NYHA, New York Heart Association; LBBB, left bundle branch clock; Hb, hemoglobin; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; IVS, interventricular septum; LAESD, left atrial end-systolic diameter; MR mitral regurgitation; RFP, restrictive filling pattern; ACE-i, angiotensin-converting enzyme–inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineralocorticoid receptors antagonists; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator. In bold are reported variables with significant association with the event at multivariable analysis.

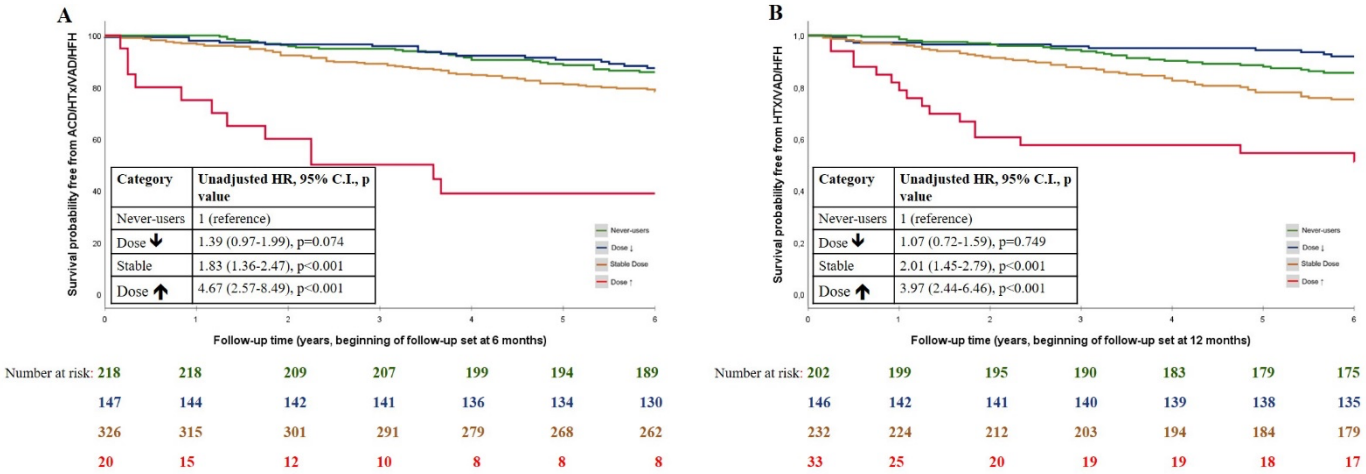
Supplementary Figure S1. Flow chart diagram of the study.



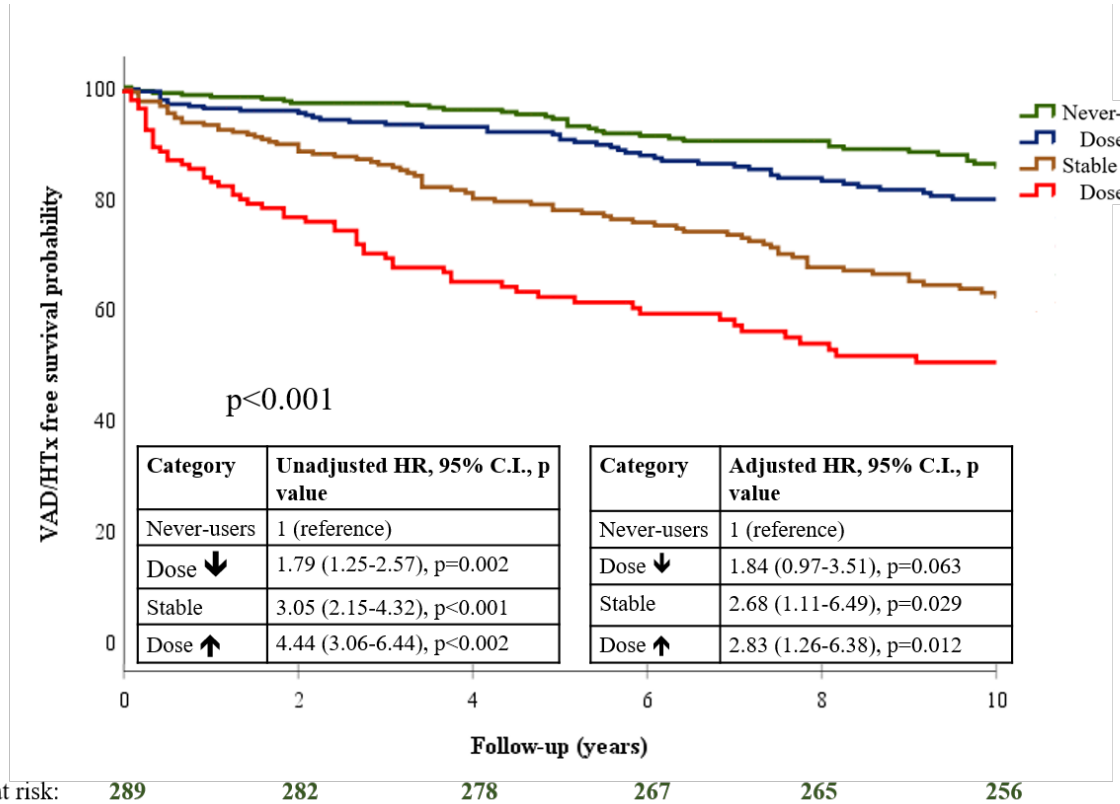
Supplementary Figure S2. Evolution of daily diuretic dose in TTNtv DCM vs non-TTNtv DCM.



Supplementary Figure S3. Kaplan Meier analysis for the primary outcome according to the loop diuretics trajectory during the first 6 months (A) and 12 months (B) of follow-up. HFH occurring before the follow-up visit were not considered. In green are represented never-users patients, in blue dose🡻 patients, in brown stable dose patients and in red dose🡹 patients. In the table are shown the HR, C.I. and p-values.



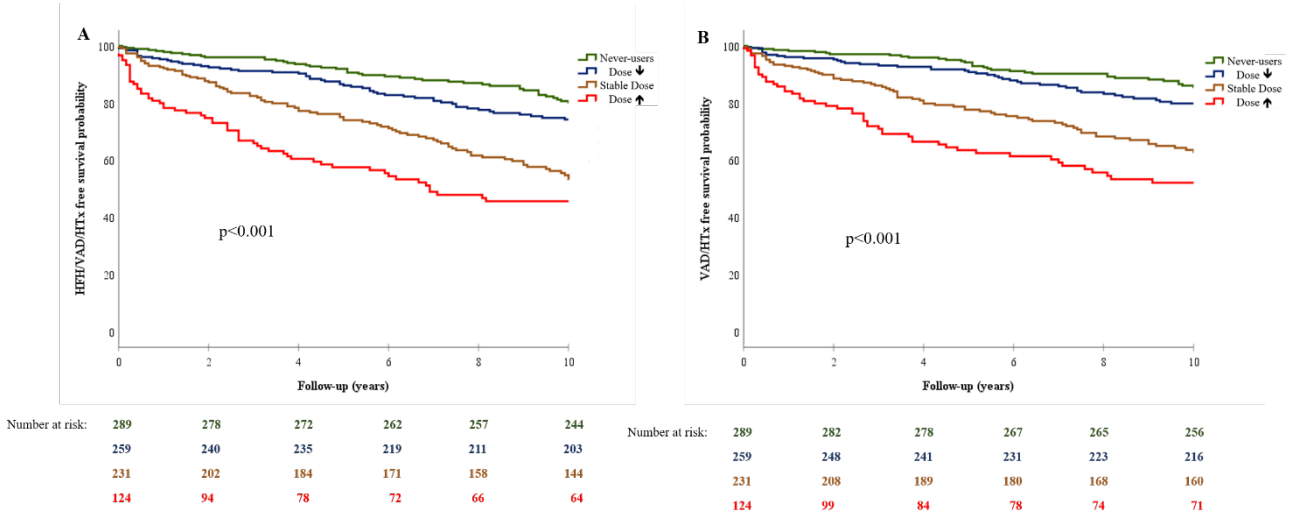
Supplementary Figure S4. Kaplan Meier analysis for secondary outcome according to the loop diuretics trajectory during the first 24 months. The beginning of the follow-up is set at 24 months (i.e. month 0 corresponds with the 24th month after enrolment in the registry). HFH occurring before the follow-up visit were not considered. In green are represented never-users patients, in blue dose↓ patients, in brown stable dose patients and in red dose↑ patients. In the tables are shown the unadjusted (left table) and adjusted (right table) HR, C.I and p-values. Details regarding multivariable model are reported in the text.



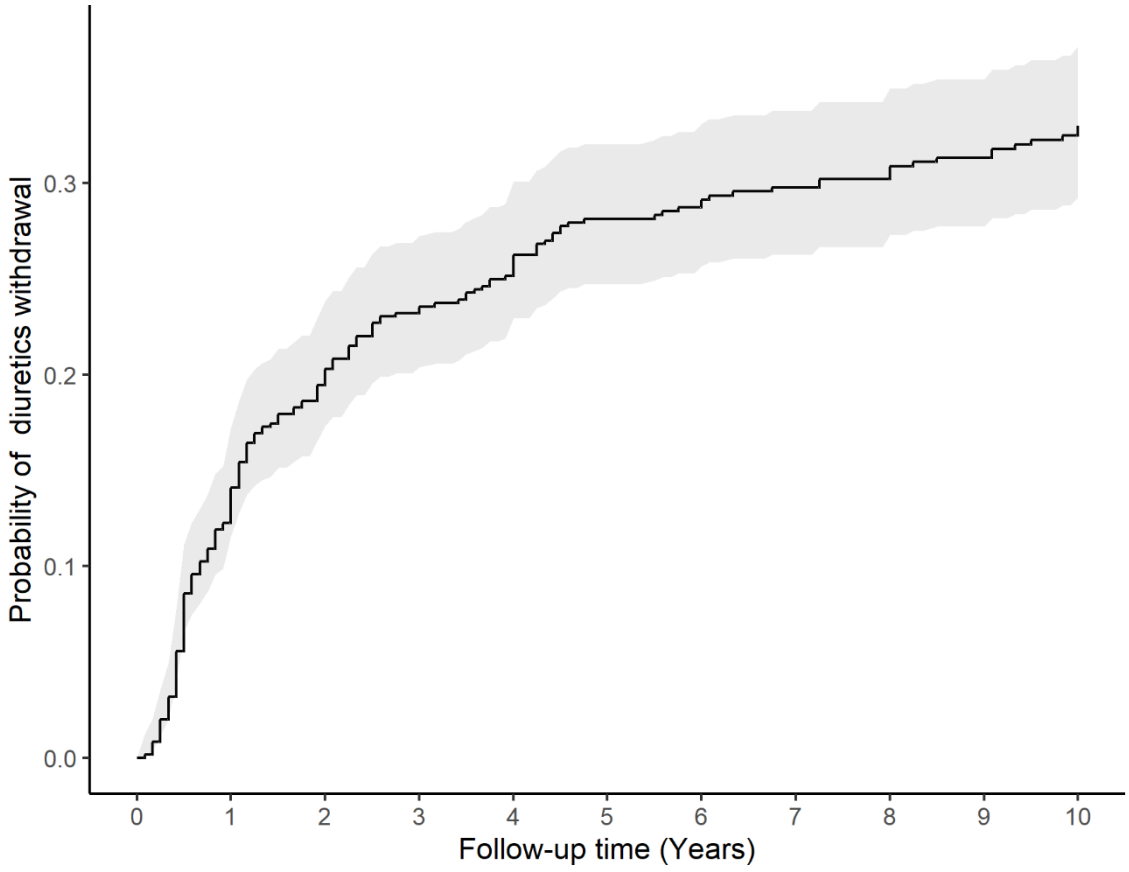
Category	Unadjusted HR, 95% C.I., p value
Never-users	1 (reference)
Dose ↓	1.79 (1.25-2.57), p=0.002
Stable	3.05 (2.15-4.32), p<0.001
Dose ↑	4.44 (3.06-6.44), p<0.002

Category	Adjusted HR, 95% C.I., p value
Never-users	1 (reference)
Dose ↓	1.84 (0.97-3.51), p=0.063
Stable	2.68 (1.11-6.49), p=0.029
Dose ↑	2.83 (1.26-6.38), p=0.012

Supplementary Figure S5. Kaplan Meier sensitivity analysis for primary (A) and secondary (B) outcome according to the diuretics dose trajectory. Baseline is set at last evaluation within 24 months observation period (i.e. month 0 corresponds with the 24th month after enrolment in the registry). Patients with heart failure hospitalization before the last evaluation before the 24th month were excluded. In green are represented never-users patients, in blue dose↓ patients, in brown stable dose patients and in red dose↑ patients.



Supplementary Figure S6. Cumulative incidence function showing the incidence of diuretic withdrawal.



Supplementary Figure S7. Kaplan Meier analysis for primary (A) and secondary (B) outcome on population on LD at enrolment, divided according to LD withdrawal. The beginning of the follow-up is set on the 24 months follow-up visit (i.e. month 0 corresponds with the 24th month after enrolment in the registry). HFH occurring within the first 24 months were not considered. In blue are represented patients undergoing diuretic withdrawal, in red are represented patients who did not stop their LD.