Incidence and factors associated with de novo atrial fibrillation in patients with wild-type transthyretin cardiac amyloidosis

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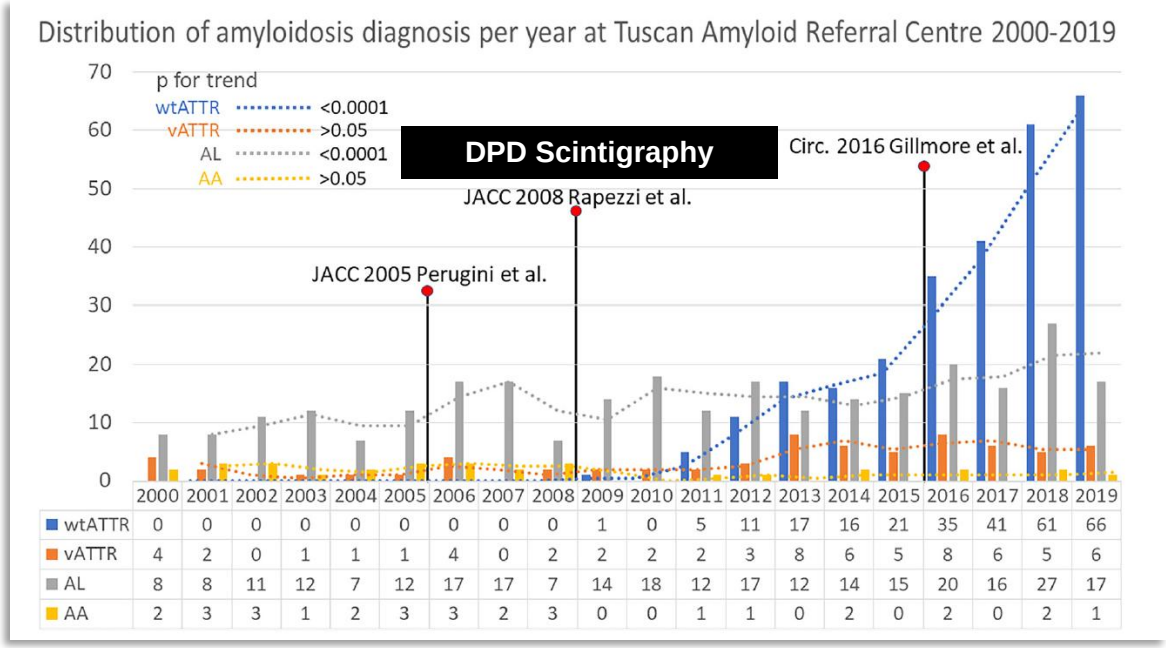
Epidemiology of ATTRwt-CA

- Wild type transthyretin cardiac amyloidosis (**ATTRwt-CA**) is an **underrecognized**, **time-dependent** and **age associated**, infiltrative cardiomyopathy caused by the extracellular deposition of insoluble protein fibrils which requires a high index of suspicion to reach definitive diagnosis.

- Although **AF prevalence is high**, the **real incidence** during long-term follow-up remains **unresolved** and warrants close monitoring of patients in sinus rhythm given high morbidity risk.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
wtATTR	0	0	0	0	0	0	0	0	0	1	0	5	11	17	16	21	35	41	61	66
vATTR	4	2	0	1	1	1	4	0	2	2	2	2	3	8	6	5	8	6	5	6
AL	8	8	11	12	7	12	17	17	7	14	18	12	17	12	14	15	20	16	27	17
AA	2	3	3	1	2	3	3	2	3	0	0	1	1	0	2	0	2	0	2	1

Zampieri et al. International Journal of Cardiology, 2021

Whether **electrocardiographic** and echocardiographic variables at ATTRwt-CA diagnosis can predict development of AF is unknown.

Study Purpose and Methods

Purpose

To describe the incidence and ECG factors associated with de novo AF in patients diagnosed with ATTRwt-CA to drive tailored arrhythmia screening.

Methods

Study design: Multicenter, retrospective, observational cohort study performed in six referral centers for CA.

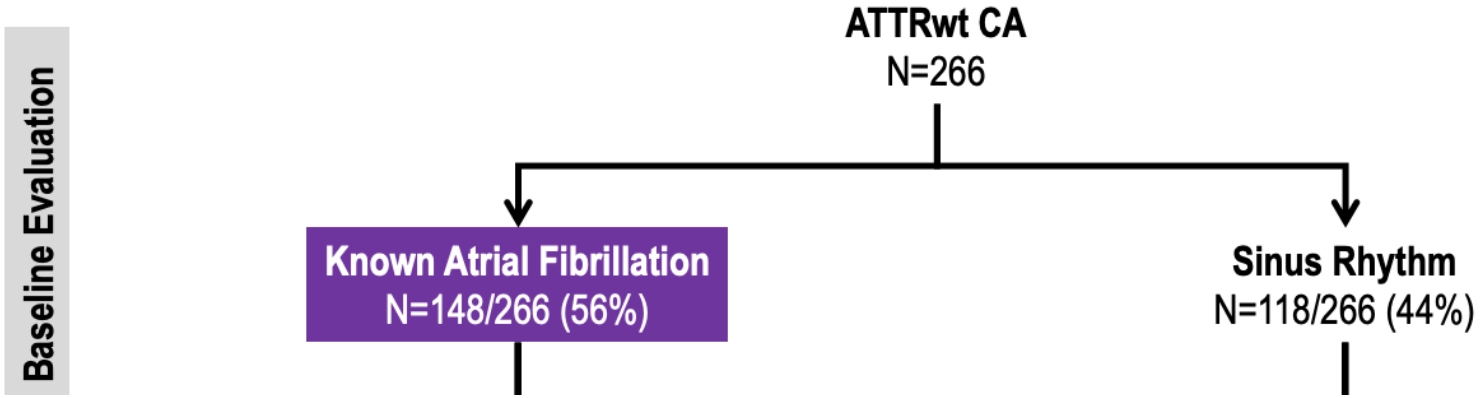
All consecutive patients diagnosed with ATTRwt-CA between 2004 and 2020 with >6-months follow up (FU) were enrolled in the study and were divided into three groups according to presence of AF:

- patients with '**known AF**';
- patients in '**sinus rhythm**' and
- patients with '**de novo AF**' at FU.

Primary Outcome

Incidence and factors associated with AF in patients with ATTRwt were the primary outcomes.

Distribution of AF in ATTRwt-CA

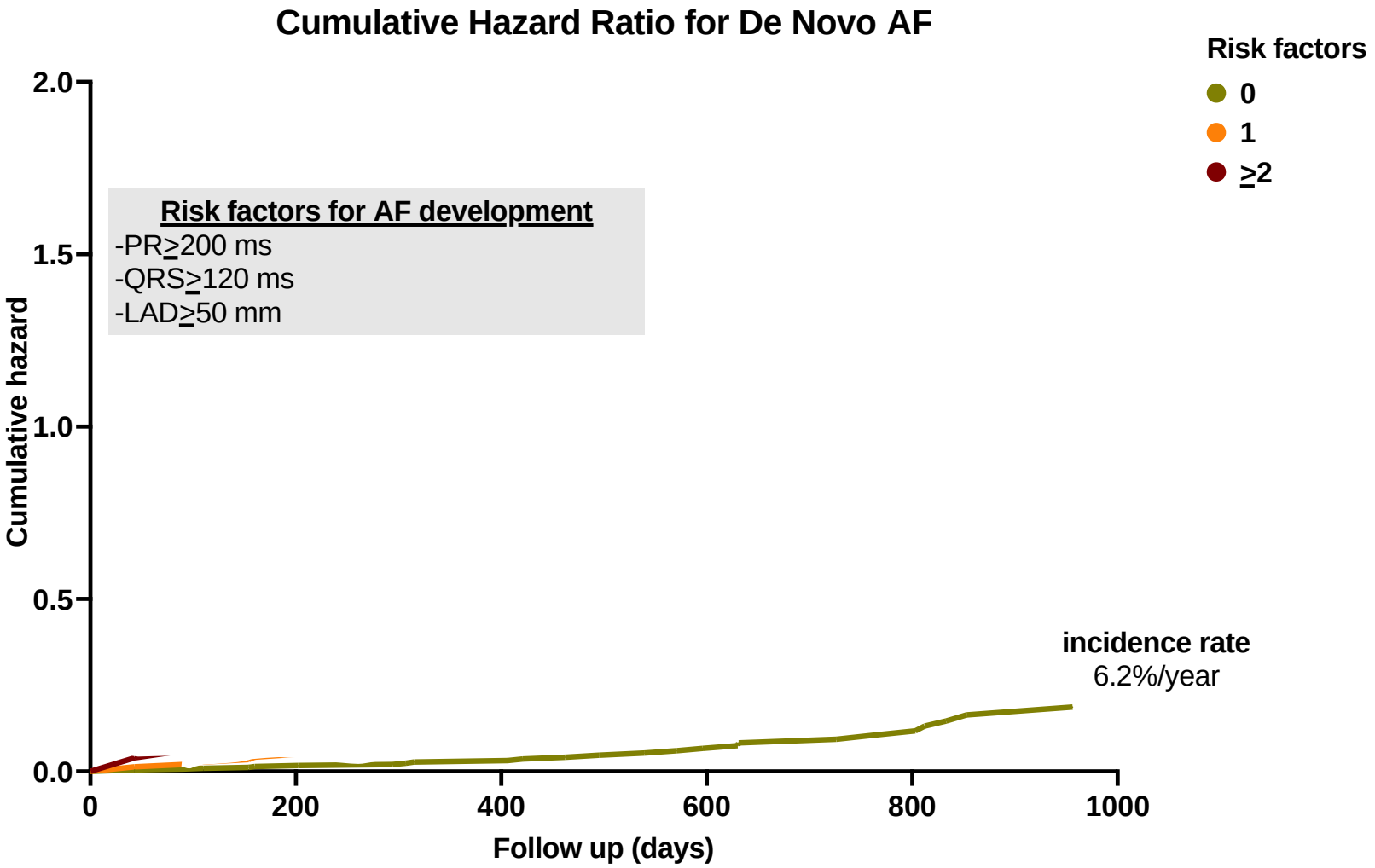


Baseline characteristics of patients diagnosed with ATTRwt according to presence of AF

	Known AF N=148	Sinus Rhythm N=84	De Novo AF N=34	p overall	p Sinus Rhythm vs De Novo AF
Gender (M), N (%)	139 (93.9)	78 (92.9)	32 (94.1)	0.943	**0.805**
Age, median [IQR], Years	81 [75-83]	81 [75-84]	79 [75-82]	0.344	**0.425**
NYHA III/IV, N (%)	48 (32)	18 (21)	1 (2.9)	<0.001	**0.012**
NTproBNP, median [IQR], pg/ml	3991 [2426-7662]	1838 [708-4734]	3402 [1362-7659]	0.006	**<0.001**
Creatinine, median [IQR], mg/dl	1.1 [1.0-1.3]	1.1 [0.9-1.4]	1.1 [0.9-1.3]	0.622	**0.376**
PR, median [IQR], ms	N=45 197 [174-240]	N=73 190 [168-220]	N=32 200 [187-245]	0.221	**0.014**
QRS, median [IQR], ms	106 [90-138]	100 [90-120]	113 [94-135]	0.092	**0.004**
LBBB, N (%)	21 (16)	7 (9.5)	4 (12.1)	0.404	**0.735**
RBBB, N (%)	26 (19.8)	13 (17.6)	9 (26)	0.511	**0.302**
Left Anterior Hemiblock, N (%)	43 (33)	29 (40.3)	15 (44)	0.169	**0.668**
Low voltages, N (%)	51 (39)	17 (23)	8 (24)	0.035	**0.628**
T wave inversion, N (%)	24 (18)	11 (15)	8 (24)	0.370	**0.173**
IVS, median [IQR], mm	18 [16-20]	16 [14-18]	19 [17-20]	<0.001	**<0.001**
Posterior wall, median [IQR], mm	16 [14-18]	15 [13-16]	16 [14-18]	<0.001	**0.015**
End diastolic diameter, median [IQR], mm	45 [41-50]	45 [43-48]	45 [42-50]	0.836	**0.994**
LV mass (index), median [IQR], g/m^2	182 [150-222]	154 [130-188]	198 [156-218]	<0.001	**0.007**
LAD, median [IQR], mm	48 [43-53]	45 [41-48]	48 [43-52]	0.019	**0.001**
LAD≥50 mm, N (%) [highest tertile]	43 (29)	12 (14)	13 (38)	0.008	**0.003**
LVEF, median [IQR], %	51 [45-60]	57 [49-63]	52 [45-60]	0.069	**0.460**
TAPSE, median [IQR], mm	16 [14-20]	20 [18-23]	19 [16-21]	0.001	**0.057**
PAP, median [IQR], mmHg	40 [28-47]	32 [30-44]	37 [37-45]	0.010	**0.209**

Factors associated with De Novo AF

Univariable and multivariable Cox regression analysis for de Novo AF onset						
Variable	**HR**	**95% C.I.**	**P**	**HR**	**95% C.I.**	**P**
PR (per Δ ms)	1.009	1.002-1.016	0.017	1.009	1.000-1.017	0.041
QRS (per Δ mm)	1.019	1.001-1.042	0.002	1.024	1.008-1.040	0.002
QRS Score (per Δ mm)	0.997	0.987-0.020	0.971	-	-	-
Low voltages (yes)	0.820	0.221-1.230	0.723	-	-	-
LAD (≥50 vs <50 mm)	2.444	1.504-5.003	0.010	2.615	1.062-6.442	0.037
IVS (per Δ mm)	1.261	1.076-1.476	<0.001	-	-	-
PW (per Δ mm)	1.141	0.891-1.357	0.137	-	-	-
LV Mass index (per Δ g/m²)	1.010	1.002-1.019	0.014	0.999	0.967-1.009	0.275
LVEF (per Δ %)	0.962	0.931-0.994	0.011	-	-	-
TAPSE (per Δ mm)	0.886	0.856-0.965	0.009	-	-	-
PAP (per Δ mmHg)	1.206	0.993-1.660	0.127	-	-	-


Cumulative Hazard Ratio for De Novo AF
Risk factors
0
1
≥2
Risk factors for AF development
-PR≥200 ms
-QRS≥120 ms
-LAD≥50 mm
incidence rate
6.2%/year
Cumulative hazard
2.0
1.5
1.0
0.5
0.0
0
200
400
600
800
1000
Follow up (days)

Conclusions

- **Prevalence of AF** in patients with ATTRwt **is high** at diagnosis **(~60%)**;
- **Incidence** of de novo AF is **12%/year**;
- **Longer PR and QRS** duration and **left atrial dilation** are associated with arrhythmia onset (40%/year if all three items are present);
- Future studies are advocated to investigate the role of **long-term ECG monitoring** (ILR?) for early AF detection and proper management in highly selected patients in sinus rhythm.

Consensus per la definizione e lo studio della fragilità e delle sindromi geriatriche nei pazienti affetto da amiloidosi cardiaca da transtiretina

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