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ORIGINAL RESEARCH

Interatrial Block Predicts Life-Threatening Arrhythmias in Dilated Cardiomyopathy

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BACKGROUND: Interatrial block (IAB) has been associated with supraventricular arrhythmias and stroke, and even with sudden cardiac death in the general population. Whether IAB is associated with life-threatening arrhythmias (LTA) and sudden cardiac death in dilated cardiomyopathy (DCM) remains unknown. This study aimed to determine the association between IAB and LTA in ambulant patients with DCM.

METHODS AND RESULTS: A derivation cohort (Maastricht Dilated Cardiomyopathy Registry; N=469) and an external validation cohort (Utrecht Cardiomyopathy Cohort; N=321) were used for this study. The presence of IAB (P-wave duration>120 milliseconds) or atrial fibrillation (AF) was determined using digital calipers by physicians blinded to the study data. In the derivation cohort, IAB and AF were present in 291 (62%) and 70 (15%) patients with DCM, respectively. LTA (defined as sudden cardiac death, justified shock from implantable cardioverter-defibrillator or anti-tachypacing, or hemodynamic unstable ventricular fibrillation/tachycardia) occurred in 49 patients (3 with no IAB, 35 with IAB, and 11 patients with AF, respectively; median follow-up, 4.4 years [2.1; 7.4]). The LTA-free survival distribution significantly differed between IAB or AF versus no IAB (both $P<0.01$), but not between IAB versus AF ($P=0.999$). This association remained statistically significant in the multivariable model (IAB: HR, 4.8 (1.4–16.1), $P=0.013$; AF: HR, 6.4 (1.7–24.0), $P=0.007$). In the external validation cohort, the survival distribution was also significantly worse for IAB or AF versus no IAB ($P=0.037$; $P=0.005$), but not for IAB versus AF ($P=0.836$).

CONCLUSIONS: IAB is an easy to assess, widely applicable marker associated with LTA in DCM. IAB and AF seem to confer similar risk of LTA. Further research on IAB in DCM, and on the management of IAB in DCM is warranted.

Key Words: dilated cardiomyopathy ■ electrocardiography ■ interatrial block ■ life-threatening arrhythmias ■ non-ischemic cardiomyopathy ■ sudden cardiac death

Dilated cardiomyopathy (DCM) is a heart disease characterized by systolic dysfunction which cannot be explained by coronary artery disease or abnormal loading conditions.[1] The disease is present in up to 1:250—mainly young—individuals and is accompanied by an increased risk of life-threatening arrhythmias (LTAs) and sudden cardiac death (SCD).[2–4] Current guidelines recommend left ventricular ejection fraction (LVEF) based algorithms to select patients who may benefit from an implantable cardioverter-defibrillator (ICD) to prevent SCD.[2,4,5] Unfortunately, it is now known that LVEF based risk-stratification is inadequate in predicting SCD, resulting in the need for novel prognostic markers in this field.[4]

Previous studies related to this topic often include promising, though not widely available markers,

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CLINICAL PERSPECTIVE

What Is new?

- While interatrial block (IAB; P-wave duration>120 milliseconds) has been independently associated with life-threatening arrhythmias (LTAs) in the general population, the prognostic value of IAB in dilated cardiomyopathy (DCM) remained unknown.
- Based on the current study, ambulant patients with DCM and IAB or atrial fibrillation confer a similar increased risk of LTAs.
- Since IAB is an easy to assess and inexpensive marker, validation of current findings potentially results in a widely available marker for the early detection of DCM individuals at risk for LTAs.

What Are the Clinical Implications?

- Physicians should pay special attention to the presence of IAB in ambulant patients with DCM given the previously observed increased risk of new-onset atrial fibrillation and the increased risk of LTAs found in current study.
- Further research on the management of patients with DCM and IAB is required. Prospective studies with (continuous) rhythm monitoring in ambulant patients with DCM will give more insights into the potential causative mechanisms between IAB, atrial fibrillation, and LTAs.
- Within these studies, special attention should be paid to the incremental value of IAB for risk stratification purposes.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
IAB	interatrial block
LTA	life-threatening arrhythmias
SCD	sudden cardiac death

including CMR-derived indexes.[4,6] While such studies will likely help to unravel underlying pathophysiological mechanisms and optimize risk-stratification in these patients, an ideal prognostic marker should also be easy to assess, widely available and preferably inexpensive to ensure clinical utility.[7]

The ECG is a well-known, inexpensive, and widely available tool. Remarkably, while an electrocardiographic assessed P-wave duration of >120 milliseconds—known as interatrial block (IAB)—has already been associated with supraventricular arrhythmias, cardiovascular and all-cause mortality,[8–10] and even LTA in the general population,[11] the association between IAB and LTA in DCM remains unknown. Here, we aimed to determine the value of IAB to predict LTA in ambulant patients with DCM using 2 independent cardiomyopathy cohorts.

METHODS

A total of 469 ambulant patients with DCM prospectively enrolled in the Maastricht Dilated Cardiomyopathy Registry between 01-2004 and 07-2017 were included in the derivation cohort (Figure 1), and 321 patients in the UNRAVEL (Utrecht cardiomyopathy Registry).[12] All patients underwent physical examination, echocardiogram, and a 12-lead ECG at baseline at the outpatient clinic as part of routine clinical care. Inclusion criteria for this study were: (i) DCM defined as a LVEF<50% with an indexed left ventricular end-diastolic diameter (LVEDDI)>33 mm/m^2 (male patients) or >32 mm/m^2 (female patients) measured by echocardiography; or a hypokinetic non-dilated cardiomyopathy (HNDC) defined as LVEF<50% with an LVEDDI≤33 mm/m^2 (male patients) or≤32 mm/m^2 (female patients) measured by echocardiography, as previously described[13]; (ii) ≥18 years of age; and (iii) written informed consent. Exclusion criteria for this study were: (i) a medical history of myocardial infarction or significant coronary artery disease; (ii) primary valvular, hypertensive or congenital heart disease; (iii) concentric hypertrophic (relative wall thickness >0.42 and LVMI≥115 in male patients or LVMI≥95 in female patients), restrictive, or peripartum cardiomyopathy or arrhythmogenic right ventricular dysplasia; (iv) no retrospectively available ambulant ECG—of sufficient quality to assess rhythm and/or perform ECG-analysis as described below—within 1 month of the first outpatient clinic visit

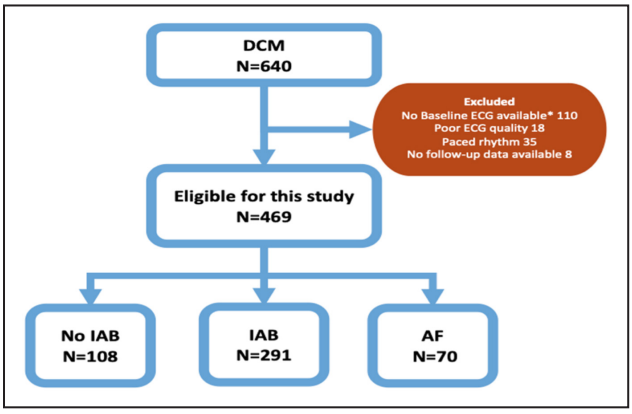

Figure 1. Patient selection for this retrospective analysis performed within the Maastricht Dilated Cardiomyopathy Registry.
All patients presented between 2004 and 2017 at the DCM outpatient clinic (OC) in the Maastricht University Medical Center. *Baseline ECG: ECG closest to OC (at the latest 1 month before or after OC). AF indicates atrial fibrillation; DCM, dilated cardiomyopathy; and IAB, interatrial block.

(baseline); (v) Paced-rhythm on baseline ECG; and (vi) no follow-up data available (vii) (on a waiting list for) a left ventricular assistant device (LVAD) or for heart transplantation (HTx) at baseline. This study complies with the Declaration of Helsinki, the study protocol was approved by the local ethics committees. Each participant of the Maastricht cohort signed informed consent at enrollment; the participants from the UNRAVEL

Table 1. Baseline Characteristics Stratified by No IAB, IAB, and AF at Baseline ECG

	Total n=469	No IAB n=108	IAB n=291	AF n=70	*P*-value
Age, y	57 [48;64]	51 [40;60]†,‡	57 [49;63]*,‡	63 [57;69]*,†	<0.001
Female sex, n%	165 (35%)	56 (52%)†,‡	98 (34%)*,‡	11 (16%)*,†	<0.001
NYHA≥III, n (%)	53 (11%)	12 (11%)	30 (10%)	11 (16%)	0.438
Family history DCM, n (%)	61 (13%)	12 (11%)	37 (13%)	12 (17%)	0.491
NT-proBNP, pmol L^{-1}	106 [39;285]	66 [18;191]‡	105 [42;284]‡	168 [82;375]*,†	<0.001
Medical history, n (%)					
HF hospitalisation	92 (20%)	20 (19%)	51 (18%)	21 (30%)	0.059
AF	109 (23.2%)	13 (12.0%)‡	31 (10.7%)‡	65 (92.9%)*,†	<0.001
Diabetes	63 (13%)	11 (10%)	44 (15%)	8 (11%)	0.380
(near) Syncope	109 (23%)	22 (20%)	69 (24%)	18 (26%)	0.679
Cardiac Arrest	10 (2%)	4 (4%)	5 (2%)	1 (1%)	0.420
Medication, n (%)					
ß-blocker	329 (70%)	71 (66%)	204 (70%)	54 (77%)	0.267
≥50%OMT	131 (28%)	19 (18%)‡	78 (27%)‡	34 (49%)*,†	<0.001
ACEi/ARB	363 (77%)	83 (77%)	222 (76%)	58 (83%)	0.493
≥50%OMT	166 (35%)	35 (32%)	108 (37%)	23 (33%)	0.608
MRA	140 (30%)	22 (20%)	94 (32%)	24 (34%)	0.047
≥50%OMT	119 (25%)	20 (19%)	81 (28%)	18 (26%)	0.164
Physical examination					
BMI, kg m^{-2}	26 [24;30]	24 [22;28]†,‡	27 [24;31]*	26 [24;30]*	<0.001
HR, bpm	75 [67;87]	76 [67;86]‡	73 [66;83]‡	89 [78;98]*,†	<0.001
SBP, mm Hg	132 [120;146]	131 [120;142]	134 [122;148]‡	130 [118;140]†	0.010
DBP, mm Hg	78 [70;86]	74 [69;84]†,‡	80 [72;88]*	80 [72;88]*	0.011
Echocardiography					
LVEF, %	31±10	34±11†	30±10*	30±9	0.007
≤35%	304 (65%)	56 (52%)†,‡	197 (68%)*	51 (73%)*	0.004
LVEDDI, mm m^{-2}	30 [28;33]	31 [29;35]‡	30 [28;34]‡	28 [26;31]*,†	<0.001
LAVI, mL m^{-2}	39 [33;53]	35 [30;42]†,‡	38 [32;52]*,‡	54 [42;68]*,†	<0.001
LVMI, gm^{-2}	108 [91;127]	100 [81;120]†	110 [96;131]*,‡	103 [87;120]†	<0.001
LVH	230 (49%)	48 (44%)	159 (55%)‡	23 (33%)†	0.003
Electrocardiography					
P-wave, ms	132 [120;144]	112 [108;116]	140 [132;148]	-	-
PR-length, ms	168 [148;184]	144 [132;157]†	175 [160;188]*	-	-
QRS, ms	124 [112;148]	116 [104;133]†	128 [116;164]*,‡	118 [112;132]†	<0.001
QRS >120 ms	140 (30%)	21 (19%)†	109 (38%)*,‡	10 (14%)†	<0.001
QTc, ms	447 [422;476]	433 [416;459]†	454 [427;481]*	441 [422;468]	<0.001
QTc, >500 ms	47 (10.0%)	8 (7.4%)	34 (11.7%)	5 (7.1%)	0.308

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; Bpm, beats per minute; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HF, heart failure; HR, heart-rate; IAB, interatrial block; LAVI, left atrial volume indexed by body surface area; LVEDDI, left ventricular end diastolic diameter indexed by body surface area; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy (LVMI≥95 in female patients or LVMI≥115 in male patients); LVMI, left ventricular mass indexed by body surface area; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association classification; OMT, percentage of optimal medical heart failure therapy; and SBP, systolic blood pressure.

*Significantly (*P*<0.05 after Bonferroni correction) different from No IAB.

†Significantly (*P*<0.05 after Bonferroni correction) different from IAB.

‡Significantly (*P*<0.05 after Bonferroni correction) different from AF (Bonferroni corrected).

cohort were included using the opt-out procedure. The UNRAVEL cohort was exempt from the Medical Research Involving Human Subjects Act (WMO) as per judgement of the Medical Ethics Committee (18/446 and 19/222 UMCU, the Netherlands), including the requirement for informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

ECG Analysis

ECG recordings (10-second, speed 25 mm/s, 12-leads, one running lead) closest to the first DCM outpatient clinic visit were obtained retrospectively from our electronic ECG reading systems (MUSE, GE Healthcare, Chicago, IL, USA) for this study. All recordings were stored as PDF-files and subsequently analyzed for the presence of IAB and atrial fibrillation (AF) using digital calipers with Autocad by a physician (H.L.M.) blinded to the study data and under supervision of A.B.G. The digital calipers were used across all leads of the ECGs to define the limits of the P-wave interval (more details are provided in Figure S1). Partial IAB was defined as P-wave duration (PWD) >120 milliseconds, and advanced IAB as P-wave duration >120 milliseconds and biphasic morphology of P-wave in leads II, III, and aVF, as previously described.[14] The defined groups (No IAB, Partial/Advanced IAB, and AF) used for downstream analysis were mutually exclusive.

Follow-Up

Patients were included from 01-2004 until 07-2017. Information regarding the occurrence of study end points (LTA) at follow-up was retrieved from the electronic medical records, municipal population register and/or telephone contact with general practitioners. From the municipal population register information is obtained whether a patient died (for routine clinical care purposes). If a patient died, and the cause of death was unclear based on the information available in the electronic medical record of our hospital, the general practitioner (or another treating physician if required) was contacted. The primary composite end point was the occurrence of LTA, defined as SCD,[15] nonfatal ventricular fibrillation (VF), hemodynamic unstable ventricular tachycardia (VT), or VT/VF with a justified implantable cardioverter-defibrillator shock or anti-tachypacing (ATP). Sudden cardiac death was diagnosed if a patient died suddenly and a potentially fatal cardiac condition was known to be present during life and/or no obvious extra-cardiac causes have been identified by post-mortem examination after sudden death and therefore an arrhythmic event was a likely cause of death.[15] Time to first event was defined as the days difference between the inclusion (first DCM outpatient clinic visit in our hospital) and the first occurrence of the primary composite study end point (LTA). Follow-up information was obtained from inclusion until January 2021. If no study end point occurred until January 2021 the subjects was censored at 01-01-2021. If the subject had a follow-up of ≥10 years and no event occurred during this period (and the subject was not loss to follow up), the subject was censored 10 years after inclusion. Additionally, patients were censored if they were referred back to the general practitioner (or to another hospital) and no reliable information about events after referral could be obtained, when a heart-transplantation (HTx) was performed, or when the patients received a left-ventricular assist device (LVAD; N=0 LVAD/HTX in Maastricht Dilated cardiomyopathy cohort; N=34/18 LVAD/HTx in the Utrecht Cardiomyopathy Cohort, UNRAVEL).

Table 2. Study End points Stratified by No IAB, IAB, and AF at Baseline ECG

	Total n=469	No IAB n=108	IAB n=291	AF n=70
Sudden cardiac death	6	1	4	1
VF/Hemodynamic unstable VT	16	2	11	3
Justified ICD Shock*	12	0	10	2
Justified ATP therapy	15	0	10	5
Combined end-point	49	3	35	11

AF indicates atrial fibrillation; ATP, anti-tachypacing; IAB, interatrial block; ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; and VF, ventricular fibrillation.

*Including 8 events for VF and 4 for VT.

Statistical Analysis

Normality was assessed visually using Q-Q-plots and histograms. Variables are displayed as mean±standard deviation, median [interquartile range], or absolute frequencies (percentage) as appropriate. Comparisons between groups were performed using chi-square tests, Fisher exact, ANOVA or Kruskal–Wallis test, as appropriate. Correlations between P-wave duration versus left atrial enlargement and PR-length were analysed using Spearman correlation. Time adjusted analysis was performed using Kaplan-Meier survival analysis with log-rank test, followed by a post-hoc log-rank test with Bonferroni correction to determine the significance of the pairwise differences between the groups (No IAB, partial and/or advanced IAB, AF). Subsequently, Cox proportional hazards analysis was performed in the derivation cohort. For the analysis in the main results, age, NTproBNP, body mass index (BMI), heart rate (HR), Systolic/Diastolic Blood pressure (SBP/DBP), LVEDDI, and LAVI were dichotomized on the median value. LVEF was dichotomized on LVEF≤35%, LVH was defined as a LVMI≥115 in male patients or ≥95 gm^{-2} in female patients.[5] QRS- and

Table 3. Baseline Characteristics Stratified by Patients Who Did and Did Not Reach the Study End Point

	Total n=469	No LTA n=420	LTA n=49	*P*-value
Age, y	57 [48;64]	57 [48;64]	53 [46;60]	0.080
Female sex, n%	165 (35%)	148 (35%)	17 (35%)	0.940
NYHA≥III, n (%)	53 (11%)	45 (11%)	8 (16%)	0.240
Family history DCM, n (%)	61 (13%)	46 (11%)	15 (31%)	<0.001
NT-proBNP, pmol L^{-1}	106 [39;285]	106 [39;283]	106 [46;320]	0.695
Medical history, n (%)				
HF hospitalisation	92 (20%)	83 (20%)	9 (18%)	0.816
Diabetes	63 (13%)	60 (14%)	3 (6%)	0.113
(Near) syncope	109 (23%)	98 (23%)	11 (22%)	0.890
Cardiac arrest	10 (2%)	8 (2%)	2 (4%)	0.318
Medication, n (%)				
ß-blocker	329 (70%)	291 (69%)	38 (78%)	0.232
≥50%OMT	131 (28%)	112 (27%)	19 (39%)	0.074
ACEi/ARB	363 (77%)	327 (78%)	36 (73%)	0.487
≥50%OMT	166 (35%)	151 (36%)	15 (31%)	0.459
MRA	140 (30%)	122 (29%)	18 (37%)	0.266
≥50%OMT	119 (25%)	104 (25%)	15 (31%)	0.373
Physical examination				
BMI, kg m^{-2}	26 [24;30]	26 [23;30]	26 [25;32]	0.208
Heart rate, bpm	75 [67;87]	76 [67;87]	74 [66;81]	0.159
SBP, mm Hg	132 [120;146]	132 [120 145]	132 [118 147]	0.542
DBP, mm Hg	78 [70;86]	80 [70;86]	75 [69;84]	0.254
Echocardiography				
LVEF, %	31±10	31±10	28±9	0.049
≤35%	304 (65%)	267 (64%)	37 (76%)	0.098
LVEDDI, mm m^{-2}	30 [28;33]	30 [28;33]	31 [29;34]	0.031
LAVI, mL m^{-2}	39 [33;53]	39 [32;52]	40 [34;58]	0.222
LVMI, gm^{-2}	108 [91;127]	107 [90;125]	120 [101;141]	0.003
LVH	230 (49%)	195 (46%)	35 (71%)	<0.001
Electrocardiography				
P-morphology				0.008
No IAB	108 (23%)	105 (25%)	3 (6%)	
IAB	291 (62%)	256 (61%)	35 (71%)	
AF	70 (15%)	59 (14%)	11 (22%)	
PR-length, ms*	168 [148;184]	168 [148;184]	172 [156;183]	0.405
QRS, ms	124 [112;148]	124 [112;148]	132 [116;168]	0.048
>120 ms	140 (30%)	119 (28%)	21 (43%)	0.036
QTc, ms	447 [422;476]	447 [422;476]	450 [420;474]	0.906
>500 ms	47 (10%)	42 (10%)	5 (10%)	0.964

ACEi indicates Angiotensin-converting enzyme inhibitor; aRB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HF, heart failure; IAB, interatrial block; LA, left atrial volume indexed by body surface area; LTA, life-threatening arrhythmia; LVEDDI, left ventricular end diastolic diameter indexed by body surface area; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy (LVMI≥95 in female patients or LVMI≥115 in male patients); LVMI, left ventricular mass indexed by body surface area; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association classification; OMT, percentage of optimal medical heart failure therapy; and SBP, systolic blood pressure.

*Patients with AF were not included for this comparison.

QTc-duration were dichotomized on 120 and 500 milliseconds, respectively. The analyses using the continuous variables instead of the dichotomized variables are shown in the supplemental material (Figure S2 and S3). All significant univariable factors associated with the outcome were added in a model on which backward selection was performed until all variables had a *P*-value of <0.05. Given the absence of a univariable significant

difference between partial IAB versus advanced IAB in the derivation cohort, these groups were merged (defined as IAB) for downstream analysis. The above-mentioned analyses were performed after imputation of missing data (total 2% missing in the Maastricht Dilated Cardiomyopathy Registry, with the most missing values for left atrial volume index [LAVI, 19%] and NT-proBNP [14%], all other variables had less than 7% missingness). Missing data were imputed using multiple imputations by chained equations with predictive mean matching (MICE-Package) creating 10 imputed data sets; the pooling of these data sets for downstream analysis was performed by applying Ruben's rule. The univariable and multivariable cox proportional hazards analysis was repeated without performing imputation (only including subjects that had no missing data to perform the univariable or multivariable analysis) to assess the consistency of the findings. A *P*-value <0.05 was considered statistically significant. Subsequently, to determine whether the univariable association between IAB and LTA could also be observed in an external ambulant DCM cohort, the before mentioned Kaplan-Meier survival analysis was performed in UNRAVEL.[12] Additionally, to visualize the association between P-wave duration as continuous variable and the 10-year risk of life-threatening arrhythmias, P-Splines were constructed within the derivation cohort and external validation cohort separately. All statistical analyses were performed using RStudio V4.0.4.

RESULTS

In total, 469 patients were included in the derivation cohort (Figure 1), 108 (23%) without IAB, 291 patients (62%) with IAB, and 70 patients (15%) with AF. All included subjects showed sinus rhythm (No IAB or IAB) or AF at baseline ECG. Patients with IAB compared with patients without IAB had a significantly higher age, body mass index (BMI), LAVI, and more often had LVH. Moreover, patients with IAB were less often female, had a longer QRS-, QTc- and PR-duration, and had a significantly lower LVEF compared with patients without IAB (Table 1). Patients with IAB compared with patients with AF were significantly younger, more often female, and had a smaller LAVI (more details are provided in Table 1). While more patients in the IAB compared with the No IAB group received ≥50% of the optimal beta-blocker dosage (based on the latest European Society of Cardioloy guidelines[5]; 27% and 18%, respectively) the difference in ≥50% optimal beta-blocker therapy dosage was only significantly different for AF (48%) versus IAB and No IAB after Bonferroni correction.

In total, 26 patients had an ICD at baseline without a significant difference between the groups (6 [6%] No IAB, 15 [5%] IAB, 5 [7%] AF; *P*=0.808). In the No IAB and IAB patients, the P-wave duration was moderately, though significantly, correlated with LAVI (rho 0.23, *P*<0.001).

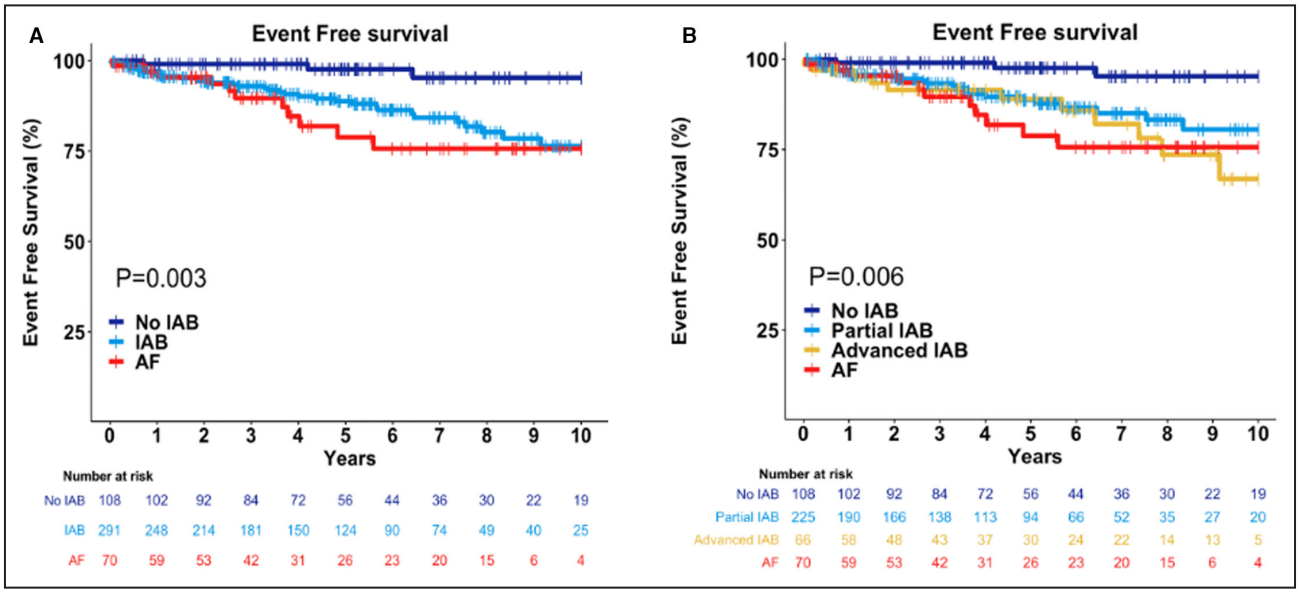

Figure 2. Kaplan–Meier curves of survival free of life-threatening arrhythmias performed within the Maastricht Dilated Cardiomyopathy cohort.

A, stratified by No interatrial block (IAB), IAB, and Atrial Fibrillation (AF). The survival distribution between the groups was significantly different (*P*=0.003, χ^2=11.5). This difference was significantly different for both IAB or AF vs No IAB (*P*=0.006 and *P*=0.001, respectively), but not for IAB vs AF (*P*=0.999) after applying Bonferroni correction. **B**, stratified by No interatrial block (IAB), Partial IAB, Advanced IAB, and Atrial Fibrillation (AF). The survival distribution between the groups was significantly different (*P*=0.006). This difference was significantly different for Partial IAB, Advanced IAB or AF vs No IAB (*P*=0.032 and *P*=0.005, 0.003, respectively), but not for Partial IAB vs Advanced IAB (*P*=0.999) after applying Bonferroni correction.

After a median follow-up of 4 [2;7] years, incident LTA (the composite primary study end point) occurred in 49 patients (N=6 SCD, N=16 Hemodynamic unstable VT/VF, N=12 justified ICD shock, N=15 justified ATP therapy; Table 2) in the derivation cohort (3 without IAB; 35 with IAB; 11 with AF, Table 2). The clinical characteristics of the patients who did and did not reach the primary end point are provided in Table 3. Patients with incident LTA had a significantly lower LVEF, more often LVH, longer QRS-duration, and more often a self-reported family history of DCM at baseline.

The univariable survival distribution was significantly different between the 3 study groups (χ^2=11.5, *P*=0.003, Figure 2A); no significant difference between partial IAB and advanced IAB was observed (Figure 2B). The survival distribution was significantly

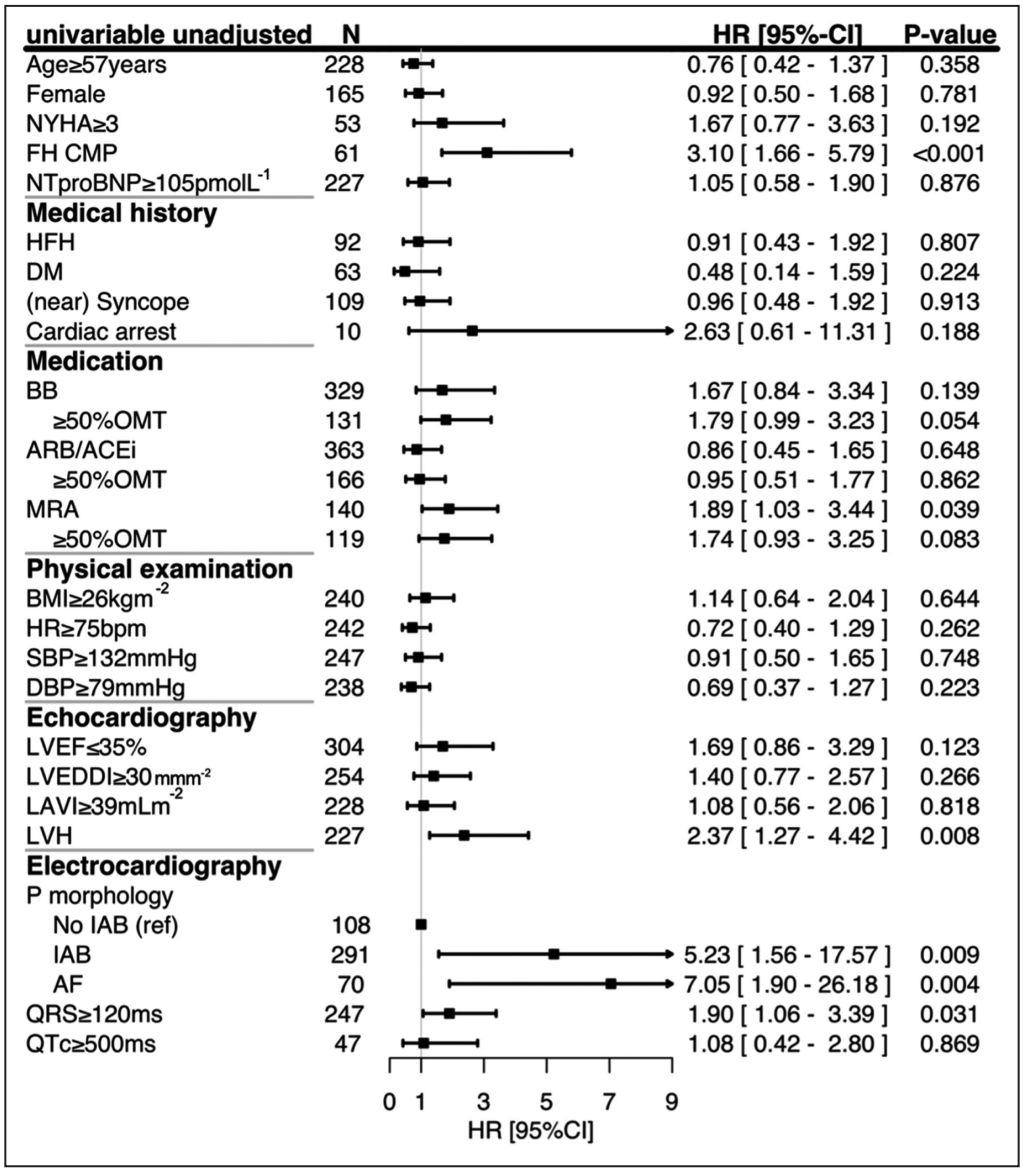

Figure 3. Univariable overview of hazard ratios (HR) for the study end point (life-threatening arrhythmias).

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; DM, diabetes; FH CMP, self-reported family history of cardiomyopathy; HFH, heart failure hospitalization; HR, heart rate; IAB, inter-atrial block; LAVI, left atrial volume index; LVEDDI, left ventricular end-diastolic diameter indexed by body surface area; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy (LVMI≥95 in female patients or LVMI≥115 in male patients); LVMI, left ventricular mass indexed by body surface area; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro hormone Brain Natriuretic Peptide; NYHA, New York Heart Association classification; OMT, percentage of optimal medical heart failure therapy in line with the ESC 2016 guidelines[5]; ref, reference; and SBP, systolic blood pressure.

different for IAB or AF versus No IAB (*P*=0.006 and *P*=0.001, respectively), but not for IAB versus AF (*P*=0.999) after applying Bonferroni correction. IAB and AF were significantly associated with the combined end point (HR=5.2 [1.6–17.6], *P*=0.009 and HR=7.1 [1.9–26.2], *P*=0.004, respectively; Figure 3). This association remained statistically significant (IAB HR=4.8 [1.4–16.1], *P*=0.013; AF HR=6.4 [1.7–24.0], *P*=0.007) in the multivariable-adjusted model (Figure 4A), which additionally included a positive self-reported family history of DCM (HR=3.2 [1.7–6.0], *P*<0.001), and LVH (HR=2.7 [1.4–5.0], *P*=0.003). The multivariable-adjusted model with partial and advanced IAB subcategories showed comparable results (Figure 4B). The univariable and multivariable cox proportional hazards analysis performed on the data set without performing imputation resulted in the same univariable associated parameters with LTA (Figure S4) compared with the imputed data set (Figure 3). Additionally, the association between IAB/AF and LTA (HR 4.6 [1.4–15.0] and HR 5.9 [1.6–21.5], respectively) remained significantly (*P*=0.012 and *P*=0.008, respectively) associated in the multivariable analysis (Figure S5). This latter analysis only included subjects that had no missing data on the significantly univariable associated parameters (N=438 in which N=46 LTA events occurred).

Given higher LAVI in patients with IAB compared with No IAB a sensitivity analysis (Figure S6) stratified by enlarged LA-volume (defined as LAVI>40, which was the median value of the included subjects) was performed. The survival distribution between IAB and enlarged LA-volume (IAB, LAVI>40) was significantly worse compared with the group with No IAB and enlarged LA-volume (No IAB, LAVI>40) (*P*=0.035). No significant difference in the survival distribution between the other groups was observed after applying Bonferroni correction (all *P*>0.05).

In total, 61 patients (13%) in the derivation cohort reported a positive family history of DCM. Patients with incident LTA more often had a positive family history of

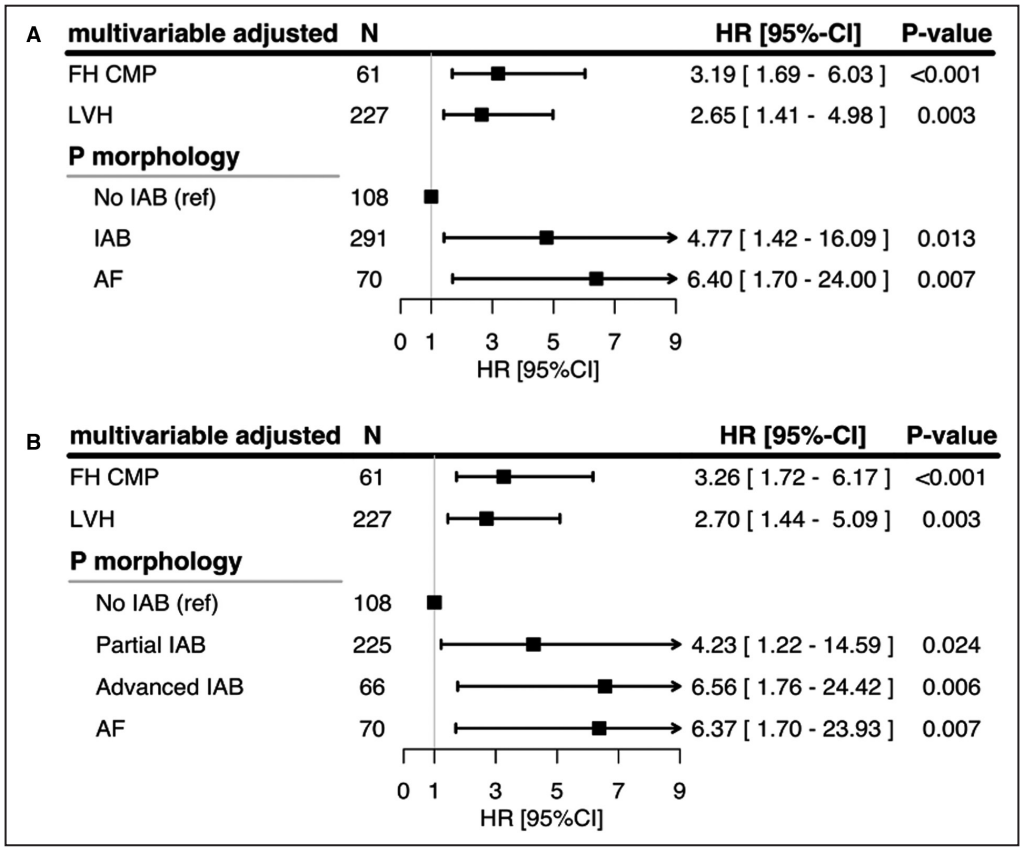

Figure 4. Multivariable overview (applying backward selection) of hazard ratios (HR) for the study end point (life-threatening arrhythmias).
A, P-morphology stratified as No IAB (PWD≤120 ms), IAB (PWD>120 ms), or AF. **B**, P morphology stratified as No IAB (PWD≤120 ms), Partial IAB (PWD>120 ms), Advanced IAB (PWD>120 ms AND biphasic morphology of P-wave in leads II, III and aVF as previously described[14]; patients with biphasic morphology of P-wave in at least III and aVF were also included in this group) or AF. AF indicates atrial fibrillation; FH CMP, self-reported family history of dilated cardiomyopathy; IAB, inter-atrial block; LVH, left ventricular hypertrophy (LVMI≥95 in female patients or LVMI≥115 in male patients); PWD, P-wave duration; and ref, reference.

DCM (15 [31%] versus 46 [11%] with no LTA, respectively; *P*<0.001). Genetic screening was performed in 245 (52%) patients as part of routine clinical care (No IAB 48%, IAB 54%, AF 51%; *P*=0.581). A (likely) pathogenic mutation (LPP; using our previously described cardiomyopathy-associated gene panel including 47 genes[16]) was found in 47 patients (10%), with no difference between the groups studied (Table S1). Additionally, no difference in the occurrence of LTA was observed in patients with and without a known LPP (*P*=0.868; Table S2).

Exploratory analysis showed that PR-length was significantly correlated with P-wave duration in the No IAB and IAB group (rho 0.64, *P*<0.001) but was univariable not associated with the occurrence of LTA during follow-up (HR=1.01 [1.00;1.02], *P*=0.16). Additionally, P-wave duration and LTA P-splines were constructed which revealed an HR=1.0 at a P-wave duration of 128 and 124 milliseconds in the Maastricht and Utrecht Cohort, respectively (Figure S7).

To determine whether the univariable association between IAB and LTA could also be observed in an external DCM cohort, the before mentioned Kaplan-Meier survival analysis was performed in UNRAVEL, including 321 ambulant patients with DCM (104 No IAB [32%], 179 IAB [56%], 38 AF [12%]). The median age was 55 [46;65], 45% were female, and the median LVEF was 30% [23;40]. The primary end point (LTA) occurred in 70 patients (13 No IAB [13%], 44 IAB [25%], 13 AF [34%]). The median follow-up duration was 3 [1;6] years. The survival distribution between the 3 groups was significantly different (*P*=0.008, χ^2=9.7; Figure 5A), and—in line with the results of the derivation cohort—no significant difference between partial and advanced IAB was observed (Figure 5B). Moreover, the difference in survival distribution was in this cohort also significantly different for IAB or AF versus No IAB (*P*=0.037 and *P*=0.005, respectively), but not for IAB versus AF (*P*=0.836) after applying Bonferroni correction.

In line with the results described above, the pooled data of the Maastricht and Utrecht cohorts showed that IAB and AF are univariable associated with LTA (HR 5.1 [1.5–16.5] and HR 6.2 [1.7–22.4], respectively; pooled survival distributions are shown in Figure S8).

DISCUSSION

This is the first study that provides insights into the prognostic association between IAB (PWD >120 milliseconds) and LTAs in patients with DCM. In both the derivation and external validation cohort, the presence of IAB at baseline was significantly associated with incident LTAs (Figure 6).

Emerging evidence suggests that AF is independently associated with LTA and SCD.[17–20] In line with these studies, we found an independent association between AF and LTA. Mechanisms that might explain the association between AF and LTA include: (i) cellular and ion-channel abnormalities involved in both AF and VF[21]; (ii) AF-related myocardial remodeling,

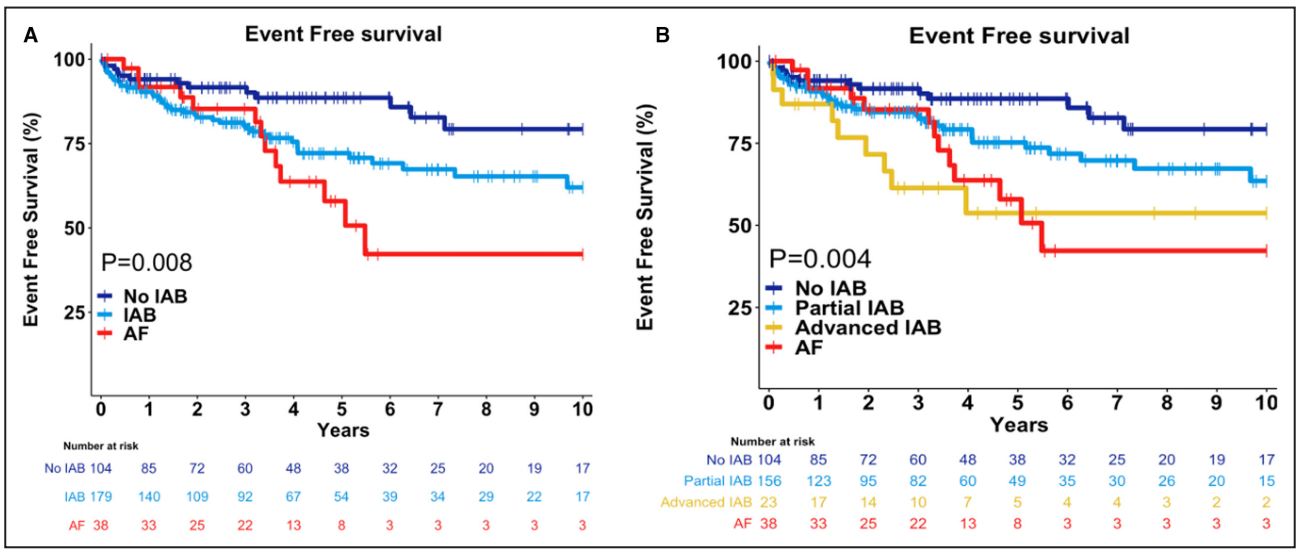

Figure 5. Kaplan–Meier curves of survival free of life-threatening arrhythmias performed within the Utrecht Cardiomyopathy cohort (UNRAVEL).
A, stratified by No interatrial block (IAB), IAB, and atrial fibrillation (AF). The survival distribution between the groups was significantly different (*P*=0.008, χ^2=9.7). This difference was significantly different for both IAB or AF vs No IAB (*P*=0.037 and *P*=0.005, respectively), but not for IAB vs AF (*P*=0.836) after applying Bonferroni correction. **B**, stratified by No interatrial block (IAB), Partial IAB, Advanced IAB and AF. The survival distribution between the groups was significantly different (*P*=0.004). This difference was significantly different for Advanced IAB or AF vs No IAB (*P*=0.009 and *P*=0.010, respectively), but not for Partial IAB vs No IAB (*P*=0.211) and Partial vs Advanced IAB (*P*=0.473), after applying Bonferroni correction.

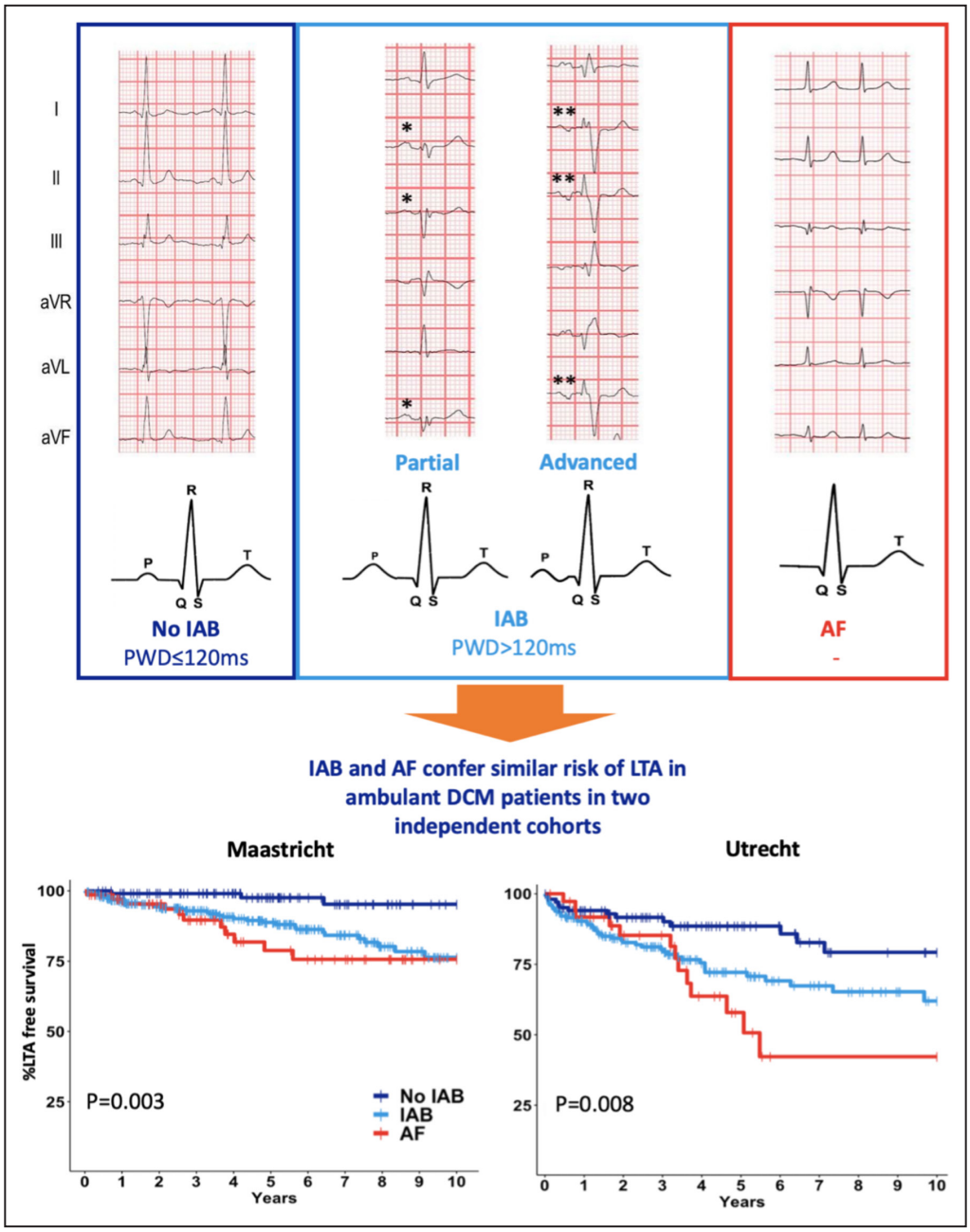

Figure 6. Interatrial block (IAB) and atrial fibrillation (AF) assessed at baseline ECG confer similar increased risk of life-threatening arrhythmias (LTAs) in ambulant patients with dilated cardiomyopathy (DCM) in 2 independent cohorts (The Maastricht DCM Cohort and The Utrecht Cardiomyopathy Cohort, UNRAVEL).

The survival distribution was significantly different for the 3 groups in both cohorts (*P*=0.003 Maastricht; *P*=0.008 Utrecht). This difference was significantly different for both IAB and AF vs No IAB, but not for IAB vs AF. *=monophasic P-wave;**=bi-phasic P-wave. PWD indicates P-wave duration.

which includes the formation of fibrosis both at the atrial as the ventricular level that could result in reentry circuits[17,22]; (iii) autonomic disturbance due to irregular ventricular beats and loss of the atrial kick resulting in increased sympathetic activity; (iv) pro-arrhythmogenic ventricular short-long-short sequences; and (v) reduced coronary perfusion due to poor rate control or due to myocardial infarction as the result of an increased prothrombotic state observed in patienst with AF.[17]

IAB and AF are known to be closely intertwined by underlying atrial myopathy.[23] Atrial dyssynchrony, fibrosis, and dilatation are processes believed to play a key role in the development and progression of atrial

myopathy and could result in IAB and eventually AF. Moreover, IAB and AF likely form a vicious circle in which IAB and AF promote atrial remodeling resulting in more severe IAB (prolongation of P-wave duration) and AF progression.[23] Given the known close association between IAB and AF, the above-mentioned mechanisms might also (partially) explain the observed association between IAB and LTA.

Whether partial IAB, advanced IAB and AF confer a similar independent risk of LTAs as suggested by current findings requires further validation in large scale multi-center prospective cohorts. Validation of current findings in such cohorts potentially can result in the detection of individuals with a lower risk of SCD, since based on current findings the absence of IAB may offer a good negative predictive value. Moreover, such studies will give more insights on how many patients diagnosed with IAB have pre-existing sub-clinical AF. Validation of current findings and incorporation in multivariable predictive models[24] in such cohorts potentially could improve decision making in the primary prevention of SCD in DCM.

Limitations

Certain study limitations must be taken into account while interpreting the results of current study, namely the retrospective study design, the absence of inter- and intra-observer variability data, the absence of follow-up information regarding new-onset atrial fibrillation, and the absence of LA-strain and other CMR assessed parameters (including midwall and left atrial Late Gandoliunium Enhancement) in current data set. Additionally, while in current study no significant difference in the association between partial and advanced and LTA was observed, this could be due to a power problem given the limited number of subjects diagnosed with advanced IAB in current study. Moreover, due to this limited power, subanalysis (including the stratification of the No IAB and IAB group by enlarged LA) should be interpreted with caution. This study does, however, give the first insights into a promising novel easy to assess and widely available marker within this field.

CONCLUSION

IAB is an easy to assess, widely applicable and highly prevalent marker for the prediction of LTA in ambulant patients with DCM. IAB and AF seem to confer similar risk of LTA. External validation of current data and further research on the management of patients with DCM and IAB is required.

ARTICLE INFOMATION

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Supplemental Material

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Figures S1–S8
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SUPPLEMENTAL MATERIAL

Table S1. Family history of DCM and overview of genetic screening performed within the Maastricht Dilated Cardiomyopathy cohort, stratified by No Inter-atrial block (IAB), IAB and AF.

	Total N=469	No IAB N=108	IAB N=291	AF N=70	p-value
Family History DCM, n (%)	61 (13%)	12 (11%)	37 (13%)	12 (17%)	0.491
Genetic sreening, n(%)	245 (52%)	52 (48%)	157 (54%)	36 (51%)	0.581
Known LPP mutation, n(%)	47 (10%)	7 (6%)	31 (11%)	9 (13%)	0.384
Known LPP TTN mutation, n(%)	23 (5%)	3 (3%)	17 (6%)	3 (4%)	0.541
Known LPP PLN mutation, n(%)	1 (0.2%)	-	1 (0.3%)	-	0.999
Known LPP LMNA mutation, n(%)	2 (0.4%)	-	2 (0.7%)	-	0.999
Known LPP FLNC mutation, n(%)	-	-	-	-	-

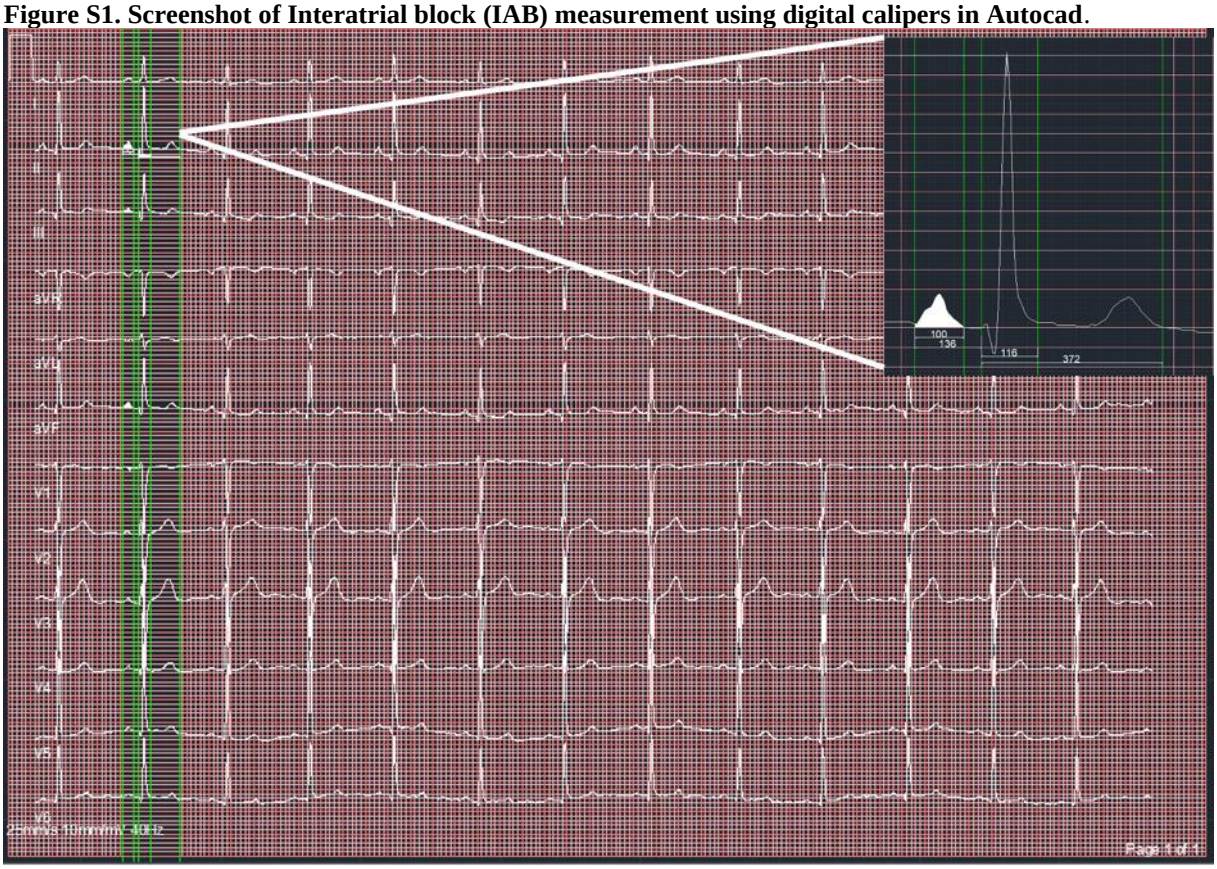
For genetic screening our previously described cardiomyopathy-associated gene panel was used (including 47 genes)[16]. Found variants were validated with Sangeq sequencing and labeled as Likely Pathogenic/Pathogenic (LPP) based on the latest criteria of the American College of Medical Genetics and the association of molecular pathology[25].
DCM= dilated cardiomyopathy; FLNC= Filamin C; LMNA= Lamin A/C mutation ; PLN= phospholamban mutation;

Table S2. Family history of DCM and overview of genetic screening performed within the Maastricht Dilated Cardiomyopathy cohort, stratified by the occurrence of Life-Threathening Arrhythmias (LTA) and No LTA.

	Total N=469	No LTA N=420	LTA N=49	p-value
Family History DCM, n (%)	61 (13%)	46 (11%)	15 (31%)	< 0.001
Genetic sreening, n(%)	245 (52%)	218 (52%)	27 (55%)	0.784
Known LPP mutation, n(%)	47 (10%)	41 (10%)	6 (12%)	0.868
Known LPP TTN mutation, n(%)	23 (5%)	20 (5%)	3 (6%)	0.946
Known LPP PLN mutation, n(%)	1 (0.2%)	1 (0.2%)	-	0.999
Known LPP LMNA mutation, n(%)	2 (0.4%)	2 (0.4%)	-	0.999
Known LPP FLNC mutation, n(%)	-	-	-	-

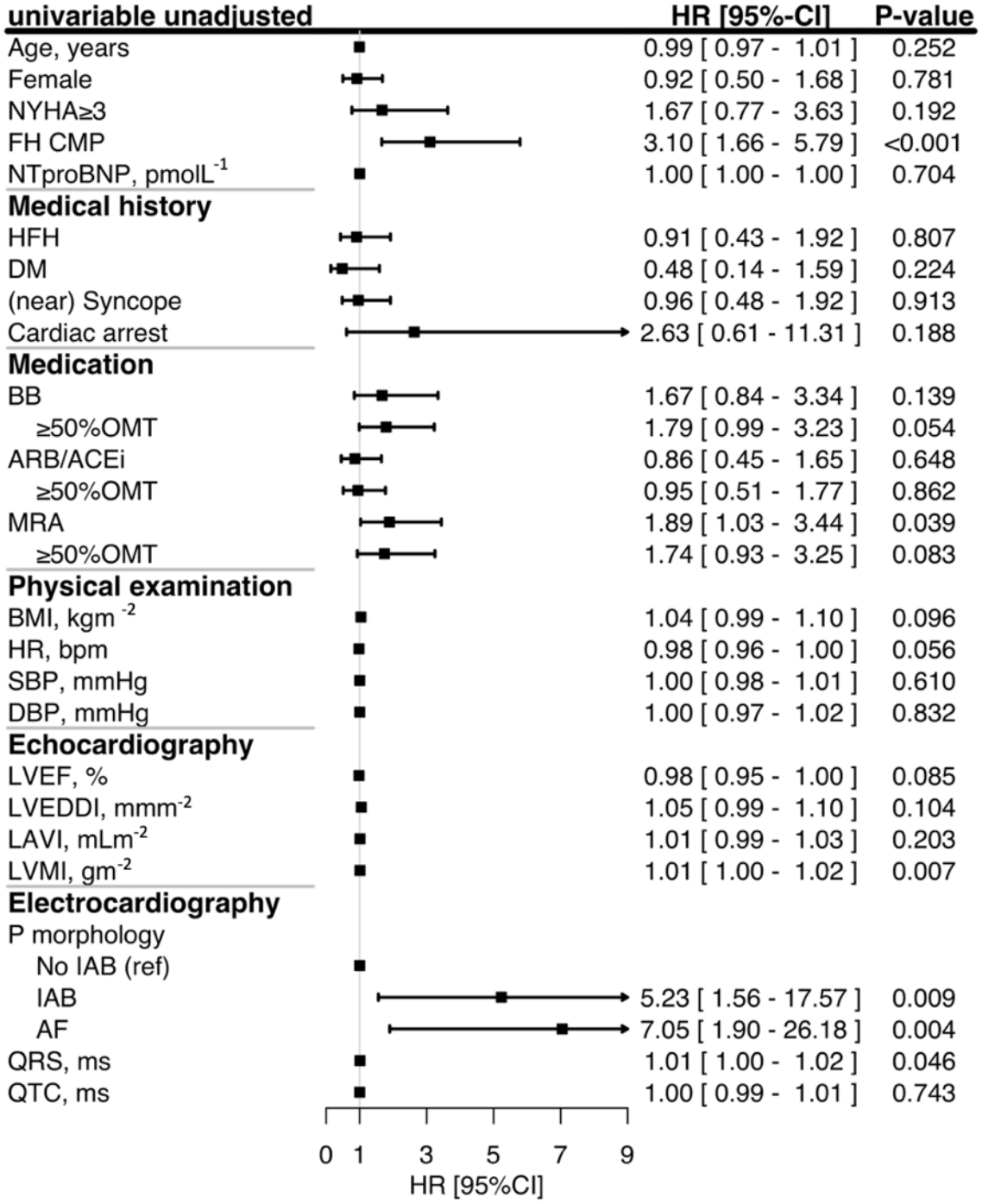
For genetic screening our previously described cardiomyopathy-associated gene panel was used (including 47 genes)[16]. Found variants were validated with Sangeq sequencing and labeled as Likely Pathogenic/Pathogenic (LPP) based on the latest criteria of the American College of Medical Genetics and the association of molecular pathology[25]. DCM= dilated cardiomyopathy; FLNC= Filamin C; LMNA= Lamin A/C mutation ; PLN= phospholamban mutation

Figure S1. Screenshot of Interatrial block (IAB) measurement using digital calipers in Autocad.



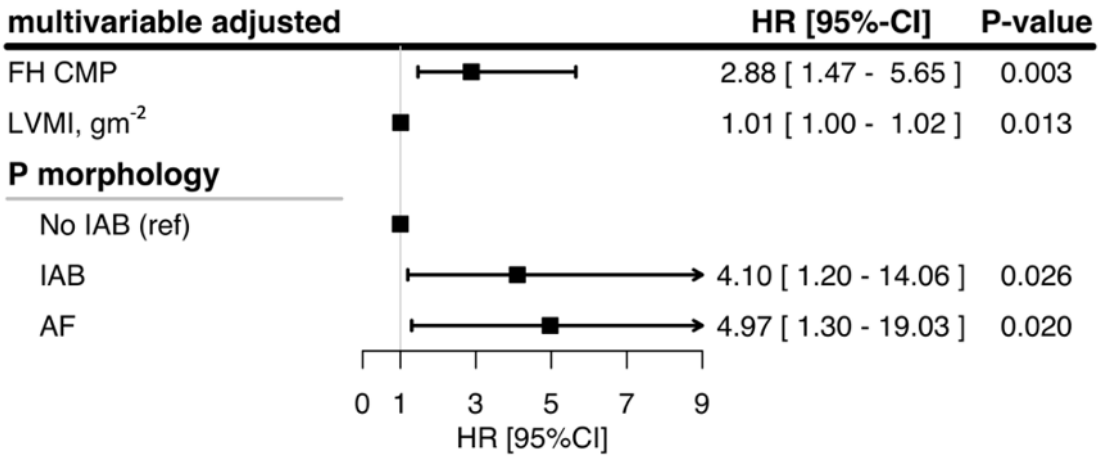
The digital calipers were used across all leads of the ECGs to define the limits of the P-wave interval. All intervals were then measured in ms: Partial IAB was defined as P-wave duration > 120 ms, and advanced IAB as P-wave duration > 120 ms and biphasic morphology (firstly positive and negative afterwards) of P-wave in leads II, III and aVF. In-between cases where a biphasic morphology was observed in leads III and aVF but not in lead II were interpreted as advanced IAB.

Figure S2. Univariable overview of Hazard Ratios (HR) for the study endpoint (life-threatening arrhythmias), all dichotomized variables variable in the main article are here shown as continuous variables.



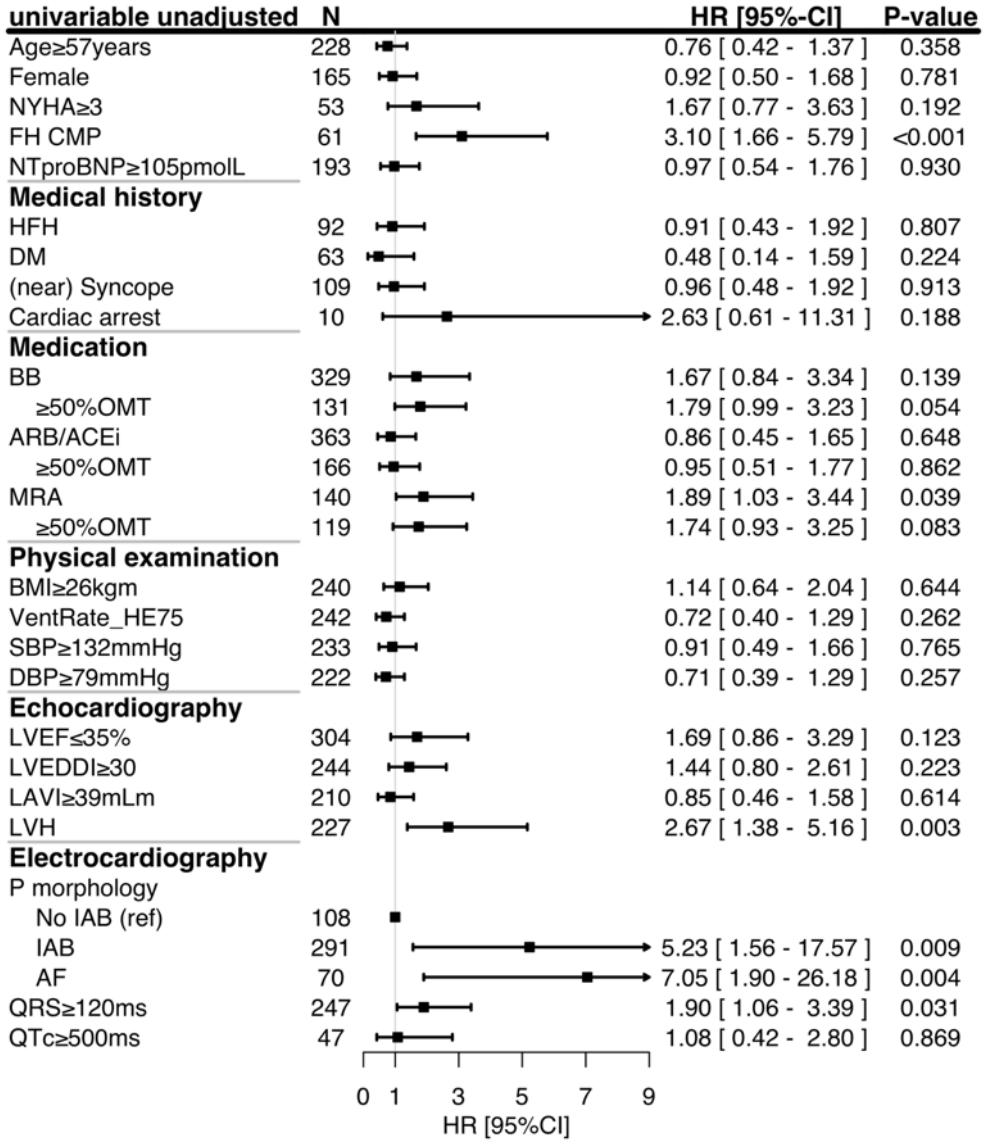
ACEi=Angiotensin-converting enzyme inhibitor; AF= atrial fibrillation; ARB=Angiotensin receptor blocker; BMI=Body Mass Index; bpm=beats per minute; CI= confidence interval; DBP=diastolic blood pressure; DCM=dilated cardiomyopathy; DM=diabetes mellitus; FH CMP=self-reported family history of cardiomyopathy; HFH=heart failure hospitalization; HR= heart rate; IAB= inter-atrial block; LAVI=left atrial volume index; LVEDDI=left ventricular end diastolic diameter indexed by body surface area; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy (LVMI≥95 in women or LVMI≥115 in men); LVMI=left ventricular mass indexed by body surface area; MRA=mineralocorticoid receptor antagonist; NT-proBNP= N-terminal-pro hormone Brain Natriuretic Peptid; NYHA=New York Heart Association classification; OMT=percentage of optimal medical heart failure therapy in line with the ESC 2016 guidelines(5); ref=reference; SBP=systolic blood pressure.

Figure S3. Multivariable overview (applying backward selection on the variables shown in Figure S2) of **Hazard Ratios (HR) for the study endpoint (life-threatening arrhythmias).**



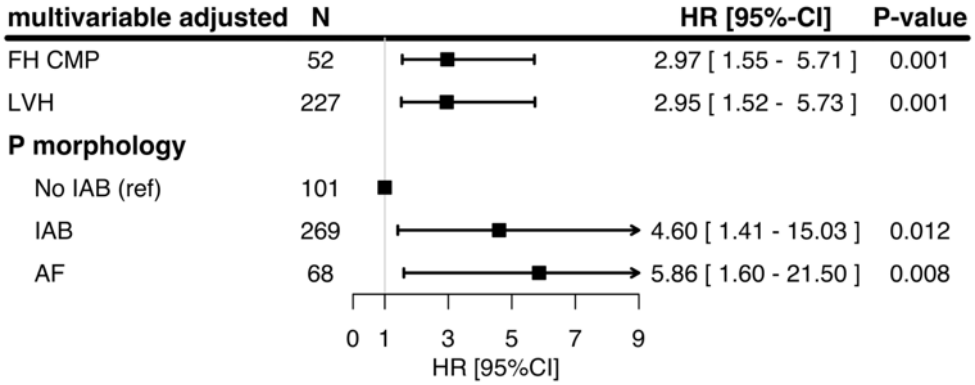
AF= atrial fibrillation; FH CMP=self-reported family history of cardiomyopathy; IAB= inter-atrial block.

Figure S4. Univariable overview of Hazard Ratios (HR) for the study endpoint (life-threatening arrhythmias) performed on the not imputed dataset of the Maastricht Dilated Cardiomyopathy Registry.



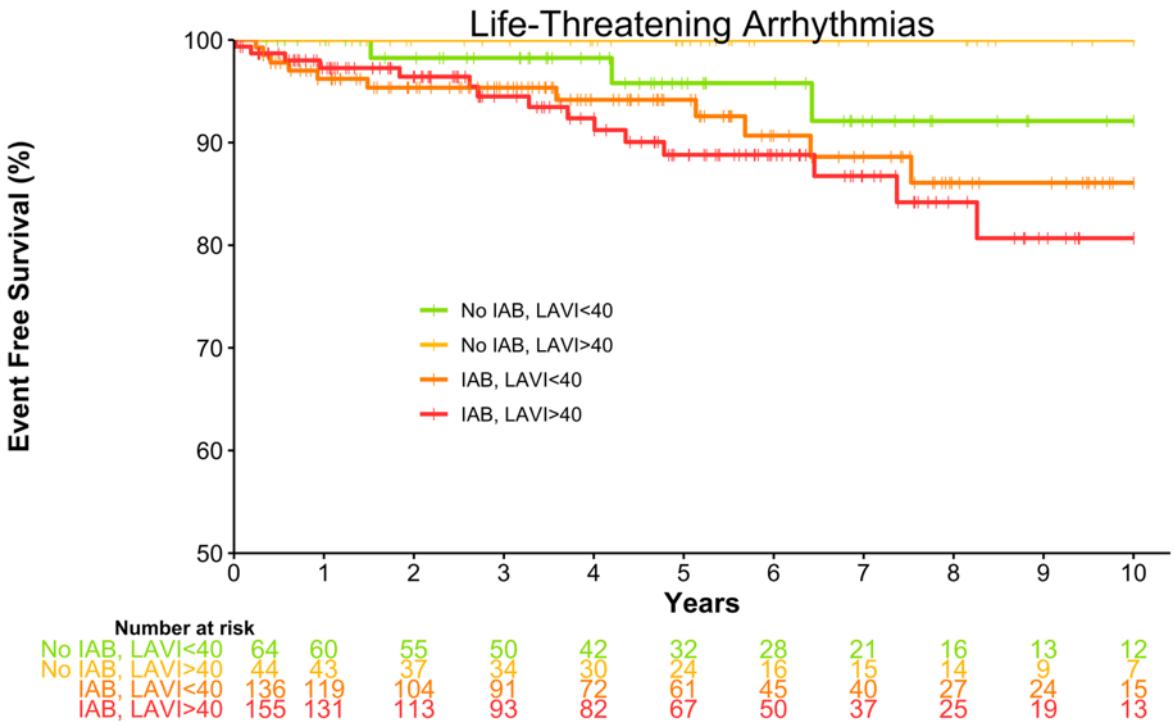
ACEi=Angiotensin-converting enzyme inhibitor; AF= atrial fibrillation; ARB=Angiotensin receptor blocker; BMI=Body Mass Index; bpm=beats per minute; CI= confidence interval; DBP=diastolic blood pressure; DCM=dilated cardiomyopathy; DM=diabetes mellitus; FH CMP=self-reported family history of cardiomyopathy; HFH=heart failure hospitalization; HR= heart rate; IAB= inter-atrial block; LAVI=left atrial volume index; LVEDDI=left ventricular end-diastolic diameter indexed by body surface area; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy (LVMI≥95 in females or LVMI≥115 in males); LVMI=left ventricular mass indexed by body surface area; MRA=mineralocorticoid receptor antagonist; NT-proBNP= N-terminal-pro hormone Brain Natriuretic Peptide; NYHA=New York Heart Association classification; OMT=percentage of optimal medical heart failure therapy in line with the ESC 2016 guidelines(5); ref=reference; SBP=systolic blood pressure.

Figure S5. Multivariable overview (applying backward selection on the dataset of subjects that had no missing data on the univariable associated variables with the study endpoint: N=438 in which N=46 LTA events occurred) of Hazard Ratios (HR) for the study endpoint (life-threatening arrhythmias),with P-morphology stratified as No IAB (PWD≤120ms), IAB (PWD>120ms), or AF.



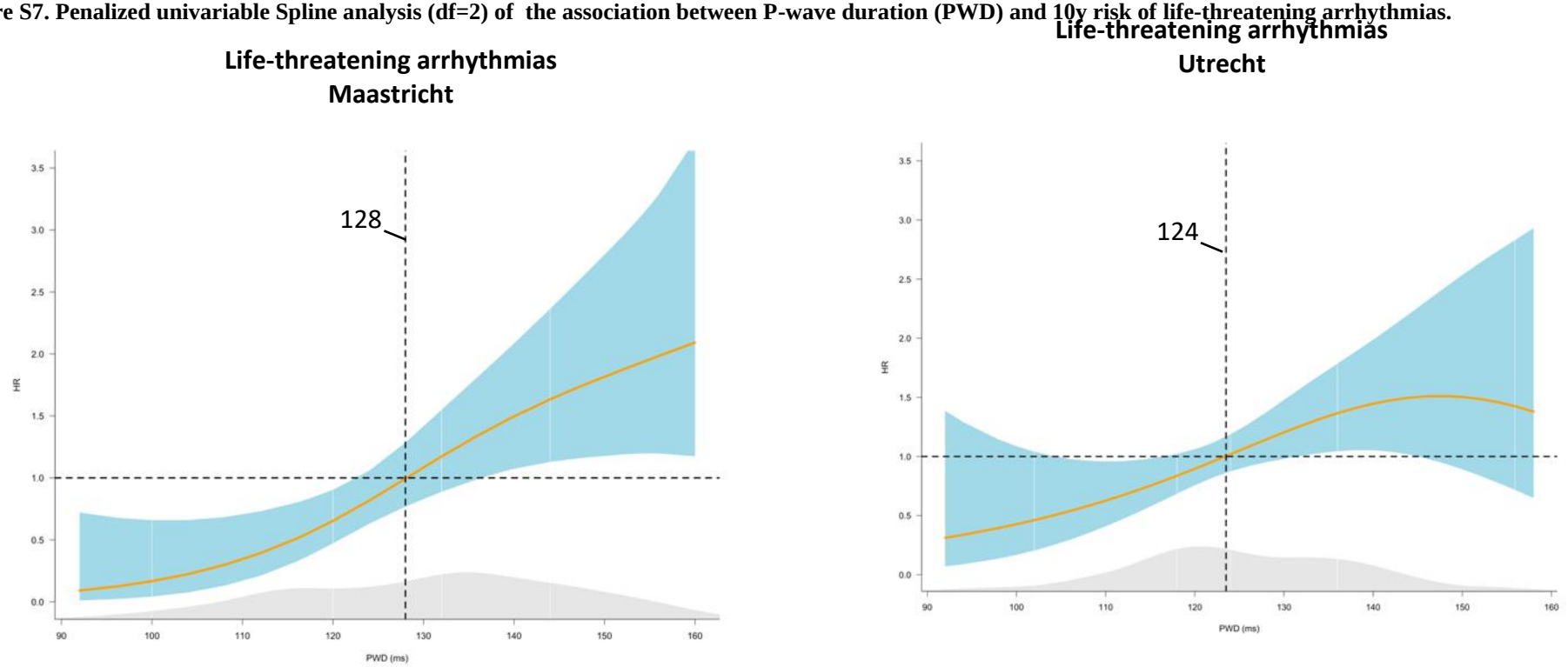
AF= atrial fibrillation; CI= confidence interval; FH CMP=self-reported family history of dilated cardiomyopathy; IAB= inter-atrial block; LVH=left ventricular hypertrophy (LVMI≥95 in females or LVMI≥115 in men); PWD= P-wave duration; ref= reference.

Figure S6. Kaplan–Meier curves of survival free of life-threatening arrhythmias stratified by the presence or absence of interatrial block (IAB), in the presence or absence of Left Atrial (LA) enlargement (defined as a Left Atrial volume indexed by body surface area higher than the median of 40 as observed in current population) in the derivation cohort.



The survival distribution was significantly (P=0.035) different for IAB with an enlarged LA (IAB, LAVI>40) compared to No IAB with enlarged LA (No IAB, LAVI>40) after Bonferroni correction for multiple comparison. No significant difference (P>0.05) was observed

Figure S7. Penalized univariable Spline analysis (df=2) of the association between P-wave duration (PWD) and 10y risk of life-threatening arrhythmias.



In the **a)** Maastricht Dilated Cardiomyopathy cohort, and **b)** Utrecht cardiomyopathy cohort (UNRAVEL). The orange line indicates the estimated hazard-ratios, blue shows the related 95%-Standard Error. The density plots at the bottom (shown in gray) show the distribution of the PWD within the cohorts. The estimated HR was equal to 1 at a PWD of 128ms and 125ms in the Maastricht Dilated Cardiomyopathy cohort and Utrecht cardiomyopathy cohort (UNRAVEL), respectively.

Figure S8. ***a)*** Kaplan–Meier curves of survival free of life-threatening arrhythmias stratified by No interatrial block (IAB), IAB, and Atrial Fibrillation (AF) performed on the **pooled data** of the **Maastricht Dilated Cardiomyopathy cohort** and the **Utrecht Cardiomyopathy cohort (UNRAVEL)**. The survival distribution between the groups was significantly different (P<0.001, $\chi 2$=16.8). This difference was significantly different for both IAB or AF vs No IAB (P=0.002 and P<0.001, respectively), but not for IAB vs AF (P=0.551) after applying Bonferroni correction. ***b)*** Kaplan–Meier curves of survival free of life-threatening arrhythmias stratified by No interatrial block (IAB), Partial IAB, Advanced IAB, and Atrial Fibrillation (AF) performed on the **pooled data** of the **Maastricht Dilated Cardiomyopathy cohort** and the **Utrecht Cardiomyopathy cohort (UNRAVEL)**. The survival distribution between the groups was significantly different (P<0.001, $\chi 2$=18.6). This difference was significantly different for Partial IAB, Advanced IAB or AF vs No IAB (P=0.012, P=0.002 , P<0.001, respectively), but not for Partial IAB vs Advanced IAB (P=0.999) after applying Bonferroni correction.