

TOPIC REVIEW

Outcomes Related to First-Degree Atrioventricular Block and Therapeutic Implications in Patients With Heart Failure



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ABSTRACT

The prevalence of first-degree atrioventricular block in the general population is approximately 4%, and it is associated with an increased risk of atrial fibrillation. Cardiac pacing for any indication in patients with first-degree heart block is associated with worse outcomes compared with patients with normal atrioventricular conduction. Among patients with heart failure, first-degree atrioventricular block is present in anywhere between 15% and 51%. Data from cardiac resynchronization therapy studies have shown that first-degree atrioventricular block is associated with an increased risk of mortality and heart failure hospitalization. Recent studies suggest that optimization of atrioventricular delay in patients with cardiac resynchronization therapy is an important target for therapy; however, the optimal method for atrioventricular resynchronization remains unknown. Understanding the role of first-degree atrioventricular block in the treatment of patients with heart failure will improve medical and device therapy. (J Am Coll Cardiol EP 2016;2:181-92)
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The electrocardiographic PR interval represents the time taken for electrical conduction from the sinoatrial node, across the right atrium, and through the atrioventricular node to the Purkinje fibers at the cardiac apex. A long PR interval (first-degree heart block) can thus result from slowing at 1 or more of these levels. It may also represent conduction through a slow, rather than a fast, atrioventricular nodal pathway. First-degree atrioventricular block (AVB) is said to be present when the PR interval measured from the surface electrocardiogram is longer than 200 ms. It has a prevalence of 1% to 2% in healthy young adults (age 20 to 30 years) (1), increasing to 3% to 4% at age 60 (2,3). It is present in up to one-half of patients with heart failure eligible for cardiac resynchronization therapy (CRT) (4,5).

First-degree AVB can lead to impaired hemodynamics (6), mitral regurgitation (7), and atrial fibrillation (AF) (8). In addition, a long PR is an adverse

prognostic marker, not only in patients with acute (9) and chronic heart failure (4), but also in those with coronary artery disease (10) and in the general population (11). In patients with chronic heart failure, those with first-degree AVB have a worse prognosis compared with patients with normal atrioventricular conduction (4,12,13). Approximately one-half of deaths in patients with heart failure are assumed to be due to arrhythmia; of those, one-half are probably due to bradycardia (14,15).

DETERMINANTS OF PR INTERVAL DURATION

The PR interval duration is determined by genetic, anatomic, and physiological factors (Central Illustration). Noujaim et al. (16) analyzed the PR interval in 33 mammalian species and found that the PR interval changes by a single order of magnitude when the body mass changes around 6-fold. In humans, the



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**ABBREVIATIONS
AND ACRONYMS****AF** = atrial fibrillation**AVB** = atrioventricular block**CRT** = cardiac resynchronization therapy**DDDR** = dual-chamber pacing mode**ECG** = electrocardiogram**ICD** = implantable cardioverter-defibrillator**MVP** = managed ventricular pacing**NYHA** = New York Heart Association**VVIR** = single-chamber pacing mode

PR interval increases progressively with age (1) and body mass index, and is longer in men compared with women (17-19). Mason et al. (17) reported the median PR interval duration in a population of 79,743 normal healthy volunteers and patients screened for enrolment in pharmaceutical company-sponsored clinical trials to be 157 ms in men (2nd and 98th percentiles: 115 to 218) and 151 ms in women (2nd and 98th percentiles: 112 to 205). The reference median for a 20-year-old man was 151 ms, and for a 90-year-old man, 188 ms.

Atrioventricular conduction is under autonomic control, which produces parallel changes in the PR interval and cycle length, that is, vagal activity increases both the cycle length and the PR interval (20). Atrioventricular

conduction is also subject to rate-related recovery effects (21), meaning that during atrial pacing, atrioventricular conduction shortens at faster pacing rates. When atrial rate is kept constant by atrial pacing, exercise shortens the PR interval (22).

Twelve percent of trained athletes have first-degree AVB, which is thought to reflect increased vagal tone (23). Atrial enlargement and fibrosis (24,25) cause slowing of atrial conduction with prolongation of the P-wave and predispose to AF (26). Medical therapy with β -blockers, amiodarone, digoxin, or non-dihydropyridine calcium channel blockers slows atrioventricular conduction, which may limit their use in the presence of pre-existing AVB.

Genome-wide association studies show that there is a significant heritable contribution to PR interval duration. In individuals from Iceland, heritability of the PR interval duration was 40%, and 4 loci for PR interval duration were identified (*TBX5*, *SCN10A*, *CAV1*, and *ARHGAP24*) (27). A study in a South Pacific Islander population showed 34% heritability of the PR interval and an association with common variants in *SCN5A* (28). A meta-analysis of genome-wide association studies from 7 community-based studies identified 9 loci associated with PR interval duration (*MEIS1*, *SCN5A/SCN10A*, *ARHGAP24*, *NKX2-5*, *CAV1/CAV2*, *WNT11*, *SOX5*, *ARHGAP24*, and *TBX5/TBX3*) (29). Five of the 9 loci were also associated with AF, but without a consistent direction of effect. Similarly, in a meta-analysis of the rs7629265 variant of *SCN5A* in African Americans, there was an association between short PR interval and increased risk of AF (30).

IS A LONG PR INTERVAL ALWAYS BAD NEWS?

There is conflicting evidence regarding the significance of a long PR interval in the general population

(Table 1). In the Finish Social Insurance Institution's CHD (Coronary Heart Disease) study of 10,785 participants ages 30 to 59 from 12 different areas in Finland, 2% had a long PR interval (>200 ms). During 35 to 41 years' follow-up, PR interval was not associated with an increase in mortality, hospitalizations, or incidence of AF, heart failure, or stroke (31). In the study, 29% of participants with an initial PR >200 ms normalized their PR interval during follow-up. The authors did not report the percentage of participants who developed new PR prolongation during follow-up. An epidemiological study of PR interval duration in the 4,678 men and women in Tecumseh, Michigan, showed no increase in mortality amongst the 2% of the population with PR \geq 220 ms during mean follow-up of 4 years (3). Three other studies have similarly found first-degree AVB to be a benign condition in healthy adults (Table 1) (1,2,32). First-degree AVB in healthy adults does not progress to higher degree AVB (32).

By contrast, data from the Framingham study found that 1.6% of the general population had a PR interval >200 ms and that first-degree AVB was associated with an increased risk of all-cause mortality, AF, and pacemaker insertion at 20 years' follow-up (Table 1) (11). Magnani et al. (18) reported that subjects in the highest quartile of PR interval (\geq 182 ms) had a higher mortality than those in the lower 3 quartiles in a cohort of 7,486 subjects from the NHANES III (Third National Health and Nutrition Examination Survey) followed up for a median of 8.6 years. Surprisingly, with longer follow-up of the same cohort, only a short PR interval (<120 ms) was associated with increased all-cause mortality (Table 1). However, a greater contribution of the P-wave duration to the PR interval (P-wave duration to PR interval ratio >0.7) was associated with increased mortality both in the short and long PR interval groups. This means that a wider P-wave (presumably as a result of atrial remodeling and interatrial conduction delay) carries a higher mortality (33).

The ABC (Health, Aging and Body Composition) study among 2,722 patients ages 70 to 79 with no functional disability found an association between increasing baseline PR interval and increasing risk of incident heart failure and AF at 10 years (19). PR interval duration did not, however, affect 10-year all-cause mortality. The prevalence of first-degree AVB in the ABC study population was 12%, which may reflect the participants' older age at baseline (mean age 74 years), compared with the Framingham study (mean age 47).

Inconsistencies between studies in healthy cohorts might be attributable to different baseline characteristics (particularly age, left ventricular

hypertrophy, level of fitness, and medication), the contribution of P-wave duration, and the effect of heart rate on PR interval duration. A particular consideration is that fitter people with higher vagal tone are more likely to have a long PR interval and are less likely to have disease. They may dilute any effect among the general population of a positive relation between PR interval and cardiovascular mortality.

Whether first-degree AVB is a marker of subclinical coronary artery disease remains controversial. Rose et al. (2) found no association between first-degree AVB (PR >220 ms) and 5-year coronary heart disease mortality in 18,000 U.K. male civil servants (Table 1). Erikssen et al. (34) reported that in 1,832 middle-aged men without coronary artery disease at baseline and followed up for 7 years, the incidence of cardiovascular events (coronary heart disease death, myocardial infarction, and angina) was not significantly different in patients with at least 1 PR interval measurement ≥ 220 ms compared with those with a PR interval consistently ≤ 210 ms (Table 1). In the Seven Countries' Study, 12,770 men ages 40 to 59 had a baseline electrocardiogram (ECG). There was an excess risk of developing coronary artery disease at 5 years in those with PR interval ≥ 220 ms (Table 1) (35).

AVB AND CORONARY ARTERY DISEASE

Coronary artery disease may affect perfusion of the atrioventricular nodal artery (which originates from the right coronary artery in 90% of people (36)). The interventricular conduction system is supplied by the penetrating branches of the left anterior descending coronary artery. Coronary artery disease has been etiologically linked to higher (second and third) degree AVB (37).

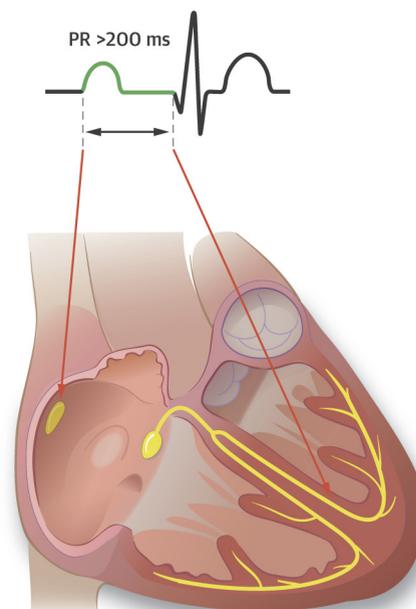
In FINCAVAS (Finnish Cardiovascular Study), the PR interval 2 min after the end of an exercise test, but not baseline PR, was a predictor of cardiovascular death during a 4-year follow-up in 1,979 patients undergoing exercise stress testing. The indication in 61% was suspected or known coronary heart disease (38). This finding may reflect atrioventricular node dysfunction becoming apparent at higher heart rates.

Data from the Duke Databank for cardiovascular disease described that in 9,637 patients with coronary artery disease, a PR interval <162 ms independently carried an increased risk of all-cause mortality, death, or stroke, and cardiovascular death or hospitalization (39). In the Heart and Soul study, Crisel et al. (10) reported a prevalence of first-degree AVB (PR >220 ms) of 9.3% in 938 patients with stable coronary artery disease. First-degree AV block was

CENTRAL ILLUSTRATION Etiology and Risks Associated With a Long PR Interval

Aetiology of First Degree AVB

- Male sex
- Increasing age
- Increased vagal tone
- Genetic factors
- Medication
- Right atrial fibrosis
- Right atrial enlargement
- Atrioventricular node conduction delay
- Bundle branch/Purkinje fiber delay



ADVERSE EFFECTS IN SPECIFIC POPULATIONS

General Population	Heart Failure*
↑ Increased risk of: • Atrial fibrillation	↑ Increased risk of: • Mortality • Hospitalization
Cardiac Pacing*	CRT*
↑ Increased risk of: • Atrial fibrillation • Death • Hospitalization	↑ Increased risk of: • Mortality • Hospitalization

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*Data are derived from post hoc subgroup analyses. AVB = atrioventricular block; CRT = cardiac resynchronization therapy.

TABLE 1 Prevalence and Outcomes Related to First-Degree AVB in Population Studies

First Author (Year) (Ref. #)	Study Type	Population	N	First-Degree AVB (ms)	First-Degree AVB, n (%)	Age (yrs)	Mean F/U (yrs)	Outcomes Related to First-Degree AVB	Notes
Nielsen et al. (2013) (8)	Registry analysis	ECG Copenhagen study 2001-2010	288,181	≥95% percentile	15,262 (5)	54*	5.7*	26% increased risk of AF compared to 40th-60th percentile	21% increased risk of AF when PR <5th percentile compared to 40th-60th percentile
Rose et al. (1978) (2)	Registry analysis	NHS Central Register, U.K. male civil servants	18,403	≥220	440 (2)	40-64	5	No increase in 5-year CHD mortality	
Soliman et al. (2009) (54)	Registry analysis	Atherosclerotic Risk in Communities study 1987-1989	15,429	Continuous variable	N/A	54	6.97	41% increased risk of AF for 1-SD increase in PR	As a categorical variable (95th percentile as cutoff) PR was not associated with AF
Blackburn et al. (1970) (35)	Registry analysis	Seven Countries Study 1958-1964	12,770	≥220	Not reported	40-59	5	Increased 5-year CHD mortality	
Aro et al. (2014) (31)	Registry analysis	Finnish Social Insurance Institution's CHD study 1966-72	10,785	>200	222 (2)	44	30	No increase in all-cause mortality	First-degree AVB normalized in 30% during F/U
Cheng et al. (2009) (11)	Registry analysis	Framingham Heart Study 1968-1971 original cohort + 1971-1974 1st offspring cohort	7,575	>200	124 (2)	46	20	Increased risk of AF, pacemaker, and all-cause mortality	
Soliman et al. (2014) (33)	Registry analysis	Third National Health and Nutrition Examination Survey 1988-1994	7,501	>200	654 (9)	59	14	No increase in all-cause mortality	PR interval <120 ms and long P-wave duration associated with all-cause mortality
Magnani et al. (2011) (18)	Registry analysis	Third National Health and Nutrition Examination Survey 1988-1994	7,486	≥182 (highest quartile)	1865 (25)	60	8.6*	Increased all-cause mortality compared to lower 3 quartiles	As a continuous variable, longer PR was not associated with all-cause mortality. Long P-wave was associated with CV mortality.
Perlman et al. (1971) (3)	Registry analysis	Tecumseh Community Health Study 1959-1960	4,678	≥220	95 (2)	≈ 40	4	No increase in all-cause mortality or new CHD	First-degree AVB normalized in 36% during F/U
Mymin et al. (1986) (32)	Registry analysis	Manitoba study 1946-1948	3,983	≥220	52 (1)	31	30	No increase in all-cause mortality	
Magnani et al. (2013) (19)	Registry analysis	Health, Aging and Body Composition Study 1997-1998	2,722	>200	339 (13)	74	10	46% increase in risk of HF	No increased risk in AF
Erikssen et al. (1984) (34)	Registry analysis	Healthy male employees in Oslo companies	1,832	≥220	98 (5)	50	7	No increase in all-cause mortality	First-degree AVB normalized to in 40% during F/U
Packard et al. (1954) (1)	Registry analysis	U.S. male pilots and flight students 1940-1942	1,000	>200	11 (1)	24	10-12	No increase in all-cause mortality or cardiac disease	

Values are mean except as noted. *Median.
AF = atrial fibrillation; AVB = atrioventricular block; CHD = coronary heart disease; CV = cardiovascular; F/U = follow-up; HF = heart failure.

associated with an increased risk of heart failure hospitalization, all-cause mortality, cardiovascular mortality, and the combined endpoint of heart failure hospitalization or cardiovascular mortality. The finding may be at least partly explained by the lower left ventricular ejection fraction and history of heart failure in the patients with AVB.

Summary points:

- The significance of first-degree AVB in healthy men and women remains uncertain. The majority of studies show that a prolonged PR interval in

middle-aged subjects is a benign phenomenon, but it may carry an increased risk in older populations, possibly as a sign of subclinical heart disease. First-degree AVB increases the risk of atrial fibrillation (discussed later).

- First-degree AVB in healthy adults does not progress to higher degree AVB.
- In the presence of coronary artery disease, a long or short PR interval may be associated with worse outcomes. It is unknown whether this relates to ischemia, anatomic remodeling, or autonomic dysfunction.

TABLE 2 Prevalence and Outcomes Related to First-Degree AVB in Heart Failure Studies (Excluding Pacing)

First Author (Year) (Ref. #)	Study Type	Population	HF	N	First-Degree AVB (ms)	First-Degree AVB, n (%)	Age (yrs)	Mean F/U (Months)	Outcomes Related to First-Degree AVB	Notes
Park et al. (2013) (9)	Registry analysis	Korean Heart Failure registry 2004–2009	Acute HF LVEF 35%* 58% NYHA III/IV	1986	>200	310 (16)	70*	18*	Adverse in-hospital outcomes when PR >200 ms was combined with QRS ≥120 ms	26% had previous history of HF
Schoeller et al. (1993) (50)	Prospective study	IDC 1982–1989	IDC LVEF <55% NYHA II–IV	94	>200	15 (18)	48	49	First- or second-degree AVB increased risk of cardiac death and sudden cardiac death	
Xiao et al. (1996) (49)	Retrospective analysis	Royal Brompton 1991–1995	IDC LVEDd >6.5 cm	58	Not defined	-	58	54	Patients who died or required pacemaker had prolongation of PR during the study period	

Values are mean except as noted. *Median.

IDC = idiopathic dilated cardiomyopathy; LVEDd = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

FIRST-DEGREE AVB IN PATIENTS WITH HEART FAILURE

Heart failure is associated with widespread electrophysiological remodeling of the cardiac conduction system, resulting in reduced RR variability, prolongation of the QRS and PR intervals, and AF. Twenty percent to 35% of patients with heart failure have a long QRS (>120 ms) (40–43), and 11% develop left bundle branch block per year (44). Increasing QRS duration is associated with increasing mortality in patients with heart failure, even when left ventricular ejection fraction is normal (45). Acute and chronic heart failure are associated with prolongation of atrioventricular conduction and first-degree AVB (4,5,9).

Both in patients with underlying ischemic heart disease and those with non-ischemic cardiomyopathy, approximately one-half of arrhythmic deaths are probably bradycardic in origin, including high-degree AVB (14,46–48). Whether first-degree AVB in heart failure heralds higher degrees of AVB and a bradycardic mode of death is unknown. In a study of 58 patients with heart failure, patients who died had a progressive increase in PR and QRS interval duration compared with stable patients over a median follow-up of 4.5 years (Table 2) (49). Another study of 85 patients with idiopathic dilated cardiomyopathy identified first- and second-degree AVB as independent risk factors for cardiac death (Table 2) (50). The authors did not examine the effect of first-degree AVB on its own (18% had first-degree and 11% had second-degree AVB).

In the Korean Heart Failure registry, the prevalence of first-degree AVB (PR >200 ms) was 10%

among patients presenting with acute heart failure (26% of the patients had a previous history of heart failure) (9). First-degree AVB in combination with a long QRS predicted in-hospital cardiac death and all-cause mortality (Table 2). In the CARE-HF (Cardiac Resynchronization-Heart Failure) study, 26% of patients with chronic heart failure had PR >200 ms (4). An analysis of the COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial showed that 50% of patients eligible for CRT had first-degree AVB (PR >200 ms) (5).

Two randomized, controlled trials of CRT versus medical therapy have been analyzed for the effect of pre-existing first-degree AVB in patients with advanced heart failure. In the CARE-HF trial, both a longer native PR interval at baseline and a longer PR interval at 3 months (paced PR for the CRT group, native PR for the control group) predicted all-cause mortality and urgent hospitalization for heart failure even after adjusting for CRT (Table 3) (4). In the COMPANION trial, a PR interval >200 ms in the group assigned to medical therapy was associated with a 41% increased risk of all-cause mortality and heart failure hospitalization, whereas no increased risk was seen for patients with first-degree AVB assigned to CRT (Table 3, Central Illustration) (5).

HIGHER DEGREE AVB IN HEART FAILURE. Higher degrees of AVB can lead to sudden cardiac death in patients with heart failure. Luu et al. (14) reported that in patients with advanced heart failure awaiting cardiac transplantation, 62% of monitored unexpected sudden cardiac deaths started with bradycardia as the initial rhythm (43% sinus bradycardia, 10% high-degree AVB, and 10% electromechanical

TABLE 3 Prevalence and Outcomes Related to Patients With First-Degree Heart Block and a Pacing Indication

First Author (Year) (Ref. #)	Study Type	Population	N	First-Degree AVB (ms)	First-Degree AVB, n (%)	Age (yrs)	F/U (Months)	Outcomes Related to First-Degree AVB	Notes
Patients with preserved systolic function									
Holmqvist et al. (2014) (60)	Subanalysis	MODe Selection Trial Sick Sinus Syndrome DDDR vs. VVIR	1,537 (779 DDDR)	>200 (baseline)	375 (25)	74	33	Increased risk of the composite death/stroke/HF hospitalization with long PR. Neither mode eliminated the negative effects of first-degree AVB	
Nielsen et al. (2012) (68)	Subanalysis	DANPACE DDDR vs. VVIR	1,357 (650 DDDR)	PQ >180 (baseline)	574 (42)	73	43	Longer baseline PQ is associated with increased risk of AF	Excluded: PR \geq 220 age <70 yrs PR \geq 260 age \geq 70 yrs
Dual-chamber pacing in patients with systolic dysfunction									
Kutalek et al. (2008) (80)	Subanalysis	DAVID trial DDDR ICD vs. VVI ICD LVEF 27% 12% NYHA III/IV	504	>200	91 (18)	65	8	DDDR is not superior to VVI pacing in patients with HF and ICD irrespective of the presence of first-degree AVB	Higher % ventricular pacing in the DDDR group
Sweeney et al. (2010) (81)	Subanalysis	DDDR MVP vs. VVI LVEF 35%, 19% NYHA III/IV 12% LBBB	1,031	\geq 230	156 (15)	63	29	Increase risk of the combined all-cause mortality/HF hospitalization/HF urgent care with DDDR MVP compared with VVI when PR \geq 230	No difference in % ventricular pacing between groups
Patients with systolic dysfunction and indication for CRT									
Olshansky et al. (2012) (5)	Subanalysis	COMPANION CRT vs. OMT LVEF 23%* NYHA III/IV	1,520 (1,212 CRT)	\geq 200 (baseline)	792 (52)	66	12 OMT/16 CRT	OMT group: 41% increase in risk of the composite all-cause mortality/HF hospitalization when baseline PR \geq 200	
Gervais et al. (2009) (4)	Subanalysis	CARE-HF CRT vs. OMT LVEF 25%* NYHA III/IV	813 (409 CRT)	>200 (native except 3-month CRT-paced)	213 (26)	67*	29	Baseline and 3-month PR interval was associated with increased risk of the composite all-cause mortality/unplanned hospitalization	
Pires et al. (2006) (12)	Subanalysis	MIRACLE CRT vs. OMT LVEF 23%, NYHA III/IV	224	Not defined	69 (30)	64	6	Baseline first-degree AVB predicted nonresponse to CRT	
Hsing et al. (2011) (88)	Subanalysis	PROSPECT-ECG Multicenter observational study	426	Continuous variable	N/A	68	6	Baseline PR interval did not predict response to CRT	
Kutyifa et al. (2014) (90)	Subanalysis	MADIT-CRT CRT-D vs. ICD QRS \geq 130 non-LBBB LVEF 30%* NYHA I/II	534 (327 CRT-D)	\geq 230 (baseline)	96 (18)	66	29	ICD-group: 3-fold increase in combined all-cause mortality/HF with baseline PR \geq 230. CRT-D conferred a 73% risk reduction in all-cause mortality/HF when PR \geq 230 compared with ICD	Current indication for CRT-D: QRS \geq 150 non-LBBB
Kronborg et al. (2010) (13)	Registry analysis	Danish Pacemaker Register, 1997-2007, CRT and CRT-D LVEF 25%* 83% NYHA III/IV	659 (225 CRT-D)	>200 (baseline)	208 (47)	66*	30*	Entire CRT group: long PR predicted all-cause-mortality and cardiac mortality	
Lee et al. (2014) (89)	Retrospective analysis	Patients with CRT, single center	403	>200 (baseline)	204 (51)	67	53	PR >200 was an independent predictor of worse response to CRT compared with \leq 200, but not associated with an increase in all-cause mortality	
Januszkiewicz et al. (2015) (87)	Retrospective analysis	Patients with CRT, single center	283	\geq 200 (baseline)	125 (44)	66	30	PR >200 was associated with an increased risk of HF hospitalization	
Patients with systolic dysfunction without indication for CRT									
Joshi et al. (2015) (91)	Subanalysis	ReThinQ, CRT vs. no-CRT, QRS <130, LVEF 15%, NYHA III	87	\geq 180 (baseline)	41 (47)	60	24	CRT group: increase in V_{O_2} max and LVEF at 6 months when PR \geq 180	No-CRT group not included in the analysis

Values are mean except as noted. *Median.

CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; DDDR = dual-chamber pacing; ICD = intracardiac defibrillator; LBBB = left bundle branch block; MVP = managed ventricular pacing; NYHA = New York Heart Association functional class; OMT = optimal medical therapy; RV = right ventricle; VVI = right ventricular pacing; other abbreviations as in Tables 1 and 2.

dissociation). In one-half of these bradycardic deaths, a precipitating cause could be identified at post-mortem (coronary artery event, pulmonary embolism, hyperkalemia, hypoglycemia), whereas the other one-half were unexplained.

In patients with advanced heart failure who presented with syncope, approximately one-half had an arrhythmic cause of which 14% had high-degree AVB (51), so high-degree AVB was the cause in 7% of patients with advanced heart failure who presented with syncope. During outpatient 2-week ambulatory monitoring in elderly patients with heart failure (mean ejection fraction $49 \pm 13\%$), 6% had high-degree AVB (52). The CARISMA (Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction) trial included 297 patients after acute myocardial infarction with ejection fraction $\leq 40\%$, who had a loop recorder implanted. Ten percent of patients developed higher degree AVB 51 to 275 days after implantation, of whom only a third were symptomatic (48). Higher degree AVB was the strongest predictor of all-cause mortality and cardiac death. In a further analysis of the same population, reduced heart rate variability and nonsustained ventricular tachycardia on 24-h Holter monitoring 6 weeks after acute myocardial infarction were independent predictors of higher degree AVB (53).

Summary points:

- First-degree AVB is common in heart failure.
- Evidence from CRT trials shows that the presence of first-degree AVB carries a worse prognosis in heart failure with or without CRT.
- Higher degrees of AVB are common in heart failure and may lead to bradycardic death.

FIRST-DEGREE AVB AS A RISK FACTOR FOR AF

Both longer PR interval (8,11,54-56) and P-wave duration (54,57) are predictors of incident AF in the ARIC (Atherosclerosis Risk In Communities), Framingham, and the Copenhagen ECG studies (Table 1). Soliman et al. (54) described an association between increasing PR interval (when considered a continuous variable) and the risk of AF in the population of the ARIC study, which recruited a random sample of residents, ages 45 to 64 years, in 4 U.S. communities. There was a 41% increase in AF risk with each standard deviation increase in PR interval duration and a 64% increase in AF risk with each standard deviation increase in P-wave duration. An increased risk of AF with PR interval ≥ 95 th percentile was found in men and women referred for ECG by their general practitioner in the Copenhagen ECG study, whereas a short

PR interval (≤ 5 th percentile) carried an increased risk of AF for women, but not men (8). A meta-analysis of 328,932 people found that increasing PR interval duration is an independent risk factor of incident AF (56). In addition, a long PR interval after radio-frequency ablation of AF predicts future recurrence of AF (58).

PACING IN THE PRESENCE OF FIRST-DEGREE AVB

In patients with first-degree AVB and PR intervals of < 300 ms, pacemaker implantation is rarely justified, unless the patient is symptomatic or has another indication for pacing (59). The presence of first-degree AVB in patients who require pacing for another indication increases the proportion of the time the patient spends with ventricular pacing (60-62). Right ventricular apical pacing can lead to a reduction in cardiac output and to left ventricular dysfunction (63,64). The risk is dependent on the proportion of the time there is ventricular pacing (percentage ventricular pacing) (65). Both ventricular and atrial pacing also increase the risk of AF (66,67).

In the MOST trial (MMode Selection Trial), in patients with sinoatrial node dysfunction, both ventricular (VVIR) and dual-chamber pacing (DDDR) increased the risk of heart failure hospitalization and AF (67). Percentage ventricular pacing was greater in the DDDR group and it was a predictor of heart failure hospitalization and AF in both the DDDR and VVIR groups. In a subanalysis of MOST, first-degree AVB was associated with an increase in the risk of the composite of death/stroke/heart failure hospitalization, irrespective of mode of pacing or percentage of ventricular pacing (Table 3) (60). Data from the DANPACE trial (Danish Multicenter Randomized Trial on Single Lead Atrial Pacing vs. Dual Chamber Pacing in Sick Sinus Syndrome) showed that longer baseline PQ interval is associated with higher incidence of AF in patients with sick sinus syndrome, which was also independent of percentage of ventricular pacing (Table 3, Central Illustration) (68).

Dual-chamber pacing preserves right atrioventricular synchrony in the presence of AVB but may not restore left atrioventricular synchrony if there is interatrial conduction delay. In patients requiring frequent ventricular pacing with preserved left ventricular function, biventricular pacing may be advantageous compared with right ventricular pacing to prevent pacemaker-induced cardiomyopathy, although none of the trials have shown reduction in mortality (69-74). The BioPace (Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac

Desynchronization) study randomized patients with AVB and mean ejection fraction of 55% to CRT or right ventricular pacing (75). Preliminary results presented at the 2014 European Society of Cardiology meeting reported that after 5.6 years' follow-up, there was no difference in the primary composite outcome of time to death or first hospitalization for heart failure between the 2 groups.

Summary points:

- Patients with first-degree AVB have worse outcomes with conventional single- or dual-chamber pacing for any indication.
- Biventricular pacing may be preferable to right ventricular pacing in patients with preserved ejection fraction requiring frequent ventricular pacing to prevent pacemaker syndrome, although studies have failed to show a mortality benefit.

PACING WITH FIRST-DEGREE AVB IN HEART FAILURE.

First-degree AVB is common in patients with heart failure and may be poorly tolerated due to "diastolic" mitral regurgitation and a reduction in cardiac output (50). Dual-chamber pacing in heart failure may improve hemodynamics in the short term (76), but in the long term, it leads to worse exercise capacity (77) and increased mortality (78). The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial reported that in patients with left ventricular systolic dysfunction (mean ejection fraction 27%) requiring an implantable cardioverter-defibrillator (ICD), dual-chamber pacing was associated with an increase in the composite risk of death or heart failure hospitalization compared with ventricular backup pacing. (79) The risk was dependent on percentage ventricular pacing (62), and it persisted among patients with first-degree AVB (Table 3) (80). Data from the MADIT II trial (Multicenter Automatic Defibrillator Implantation Trial II) also showed that percentage ventricular pacing >50% carried an increased risk of new or worsened heart failure and ICD therapy in patient with heart failure and previous myocardial infarction (61).

Managed dual-chamber ventricular pacing (MVP), which reduces right ventricular pacing by allowing long atrioventricular delays, is not superior to ventricular backup pacing in patients with heart failure (mean ejection fraction 35%) and ICD (81). There was no difference in percentage ventricular pacing between the MVP and backup pacing groups. Subgroup analysis showed that patients with a PR interval ≥ 230 ms had a 2.8-fold increase in risk of the combined endpoint of death or heart failure hospitalization/heart failure urgent care with MVP compared with ventricular backup pacing (Table 3).

It is possible that MVP leads to worse outcomes by allowing further prolongation of the PR interval (81). Some of the patients included in the ICD trials discussed in the preceding text would be eligible for CRT based on current recommendation (82).

Summary point:

- When patients with heart failure and first-degree AVB require an ICD, single-chamber ventricular backup pacing is superior to dual-chamber pacing, at least partly due to lower percentage ventricular pacing.

FIRST-DEGREE AVB AND BIVENTRICULAR PACING.

CRT provides atrioventricular as well as interventricular resynchronization and improves survival, left ventricular function, exercise tolerance, and quality of life compared with medical therapy in patients with heart failure, ejection fraction $\leq 35\%$, and a wide QRS (preferably left bundle branch block) (83-86). In the CARE-HF trial, first-degree AVB predicted all-cause mortality and heart failure hospitalization even after adjusting for CRT (Table 3) (4). By contrast, a subanalysis of the COMPANION trial showed that the increased risk of mortality and heart failure hospitalization associated with first-degree AVB did not persist in patients assigned to CRT (5). In a retrospective analysis of the Danish Pacemaker Register, Kronborg et al. (13) reported that in 659 patients undergoing CRT implantation, 47% had first-degree AVB and a long native PR interval was an independent predictor of all-cause and cardiac mortality (Table 3). In this study, a normal baseline PR interval predicted better response to CRT. Januszkievicz et al. (87) found an increased risk of heart failure hospitalization in patients with a PR interval ≥ 200 ms undergoing CRT implantation in a single center (Central illustration).

Pires et al. (12) reported that baseline first-degree AVB predicted nonresponse to CRT in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial (defined as no improvement or worsening in New York Heart Association [NYHA] functional class). However, in an observational study, baseline PR interval as a continuous variable did not correlate with response to CRT after adjusting for other variables (Table 3) (88). A retrospective, single-center study found that first-degree AVB was an independent predictor of worse response to CRT (89).

A retrospective, nonrandomized subanalysis of the MADIT-CRT trial suggested that patients with heart

failure and non-left bundle branch block (QRS ≥ 130 ms) benefit from CRT if they also have first-degree AVB, with reduction in the risk of all-cause mortality (90). Some of these patients would qualify for CRT under current guidance (QRS ≥ 150 ms). A subanalysis of the ReThinQ (Resynchronization Therapy in Narrow QRS) trial reported that among patients with heart failure and a narrow QRS (<130 ms) who were randomized to CRT, those with a PR interval ≥ 180 ms had improvement in V_{O_2} max, left ventricular ejection fraction, and NYHA functional class at 6 months (91). These studies indicate that patients with heart failure and first-degree AVB may benefit from CRT outside traditional indications; however, it is worth noting that these results are based on subset analyses without randomization and should be interpreted with caution.

The optimum value for atrioventricular delay remains unknown, as is the long-term outcome of atrioventricular delay optimization. Different methods for optimizing atrioventricular delay in CRT have been employed, including echocardiographic (92), device-based algorithms (93), noninvasive systemic blood pressure (94), and peak endocardial acceleration (95). A meta-analysis of clinical and echocardiographic outcomes from atrioventricular and interventricular delay optimization showed a neutral effect (96). In addition, it is unknown whether the native PR interval and optimal paced atrioventricular delay change over time. A subanalysis of the MADIT-CRT trial included 1,235 patients with mildly symptomatic heart failure and left bundle branch block implanted with CRT with defibrillator or ICD and showed that patients with a short programmed CRT atrioventricular delay (<120 ms) had a lower risk of heart failure or death compared with both those with a long programmed CRT atrioventricular delay (>120 ms) and those in the ICD-only group (97). The effect was independent of baseline PR interval (97).

In patients with heart failure and an indication for bradycardia pacing who do not meet CRT eligibility criteria, biventricular pacing is advantageous compared with right ventricular pacing (Class IIa recommendation in the European Society of Cardiology guidelines) (59,98,99). The Block-HF study recruited patients with mild-moderate symptoms of heart failure (mean ejection fraction 40% and NYHA functional class I to III) with AVB requiring a permanent pacemaker. Twenty percent had first-degree AVB, 22% had second-degree AVB, and 48%, third-degree AVB. Biventricular pacing was superior to

right ventricular pacing in reducing the primary endpoint of death, urgent heart failure care, or $\geq 15\%$ increase in left ventricular end-systolic volume index (100).

Summary points:

- Patients with heart failure and another pacing indication benefit from CRT compared with right ventricular pacing.
- The optimal method for adjusting atrioventricular delay in CRT remains unknown.

CONCLUSIONS

In the general population, first-degree AVB carries an increased risk of AF. Cardiac pacing for any indication in patients with first-degree heart block is associated with worse outcomes compared with patients with normal PR interval duration. Data from CRT studies have shown that, in patients with heart failure, first-degree heart block is associated with worse outcomes.

Limited evidence exists as to whether patients with heart failure, ejection fraction $\leq 35\%$, and first-degree AVB derive additional benefit from CRT compared with those with normal atrioventricular conduction or whether they, in fact, have worse outcomes despite CRT. If the former is true, then CRT indications could be expanded for patients with PR prolongation to include those with QRS ≤ 120 ms or ≤ 150 ms with non-left bundle branch block.

FUTURE APPROACHES TO STUDY. Unselected population studies are needed on the prevalence, incidence, and prognostic significance of first-degree AVB in heart failure. In patients with heart failure and first-degree AVB, the effect of commonly used medication that further slows atrioventricular conduction (digoxin, β -blockers, amiodarone) is unknown. The effectiveness of these therapies should be evaluated in the context of atrioventricular conduction delay.

A gap in knowledge exists when considering optimal atrioventricular delay settings after CRT implantation. No single optimization method has been shown superior to nominal settings, and studies to assess CRT outcomes at different atrioventricular intervals are needed.

The effect of different pacing sites in optimizing atrioventricular delay is unknown. When pacing for any indication in patients with pre-existing first-degree AVB, is it advantageous to pace from the atrial septum (rather than the right atrial appendage)

and/or the His bundle or right ventricular septum (rather than the right ventricular apex)? This may offer improved left-sided atrioventricular resynchronization, bypassing any coexisting conduction delay in the Bachmann's bundle or inter-ventricular septum, respectively.

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