# Effect of Left Ventricular Conduction Delay on All-Cause and Cardiovascular Mortality (from the PRECISION Trial)

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**The prognosis associated with prolonged intraventricular conduction on electrocardiogram (ECG) remains uncertain. We aimed to compare clinical outcomes of narrow versus prolonged intraventricular conduction on ECG stratified by QRS morphology and cardiovascular disease (CVD) status. A post-hoc analysis was performed of the randomized-control PRECISION trial. Patients with centrally adjudicated, nonpaced baseline ECGs were included. QRS duration was classified narrow (≤100 ms) versus prolonged (>100 ms) with additional categorization into left (LBBB) or right (RBBB) bundle branch block or nonspecific intraventricular conduction delay (IVCD). IVCD was subclassified if left ventricular conduction delay (LVCD) was present (L-IVCD) or absent (O-IVCD). The primary outcome was adjudicated all-cause and cardiovascular (CV) mortality. Of 24,081 patients randomized, 22,067 (92%) were included with follow-up 34 ± 13 months. Study patients were 63 ± 9 years, 64% female, 75% Caucasian, 23% with established CVD. The prevalence of QRS prolongation was 5.6% (1,240): 760 right bundle branch block (3.4%), 313 LBBB (1.4%), and 161 IVCD (0.7%), 95 subclassified L-IVCD (0.4%). After adjustment, LBBB and L-IVCD were similarly associated with increased all-cause (LBBB: 2.3 [1.4 to 3.8], p = 0.001; L-IVCD: 4.0 [2.1 to 7.9], p <0.001) and CV (LBBB: 3.6 [2.0 to 6.5], p <0.001; L-IVCD 3.6 [1.3 to 9.7], p = 0.001) mortality. The presence of LVCD (LBBB or L-IVCD) was associated with all-cause (2.8 [1.8 to 4.2], p <0.001) and CV (3.6 [2.2 to 6.1], p <0.001) mortality exceeding the observed risks of coronary artery disease, left ventricular hypertrophy, or diabetes. The LVCD hazard persisted across QRS durations (100 to 120 vs >120 ms) and CVD status. In conclusion, LVCD, whether LBBB or L-IVCD, was strongly associated with increased mortality in patients with and at-risk for CVD.**  **(Am J Cardiol 2019;124:1049−1055)**

Prolonged intraventricular conduction on surface electrocardiogram (ECG) is relatively common, with estimated prevalence 1% to 4%.[1−5] Delayed left ventricular conduction in the form of left bundle branch block (LBBB) is a well-established risk factor for all-cause and cardiovascular (CV) mortality, sudden cardiac death (SCD), and worsening heart failure (HF) in patients with and without pre-existing cardiovascular disease (CVD).[6−17] However, the prognosis associated with right bundle branch block (RBBB) is uncertain,[5,11,13,15,17] whereas mortality data on nonspecific intraventricular conduction delays (IVCD) are limited.[4,5] Consequently, we sought to evaluate the outcomes of patients with bundle branch blocks (BBB) and IVCD by utilizing a contemporary study population with well-characterized CVD status, central ECG analysis, and adjudicated clinical events obtained in the context of a randomized control trial. In this post-hoc analysis of the PRECISION trial,[18] we characterized mortality rates of patients with prolonged QRS duration subclassified into LBBB, RBBB, and IVCD subtypes, both with and without established CVD. We hypothesized that patients with left ventricular conduction delay (LVCD) on baseline ECG would experience higher all-cause and CV mortality from increased rates of HF and SCD.

## Methods

Institutional review board approval was obtained for a post-hoc analysis of the multicenter, double-blind, randomized-control PRECISION trial. Although participants provided informed consent for the PRECISION trial, informed consent was waived for the post-hoc analysis. PRECISION's methods and clinical outcomes have previously been published.[18,19] In summary, from 2006 to 2014, PRECISION enrolled 24,081 patients from 923 centers across 13 countries. Mean follow-up was 34(13) months. Adult patients were eligible for PRECISION if they had diagnosed osteoarthritis (OA) or rheumatoid arthritis (RA), required daily nonsteroidal anti-inflammatory drugs, and

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had either established CVD or increased risk for CVD. An independent, blinded clinical events committee at the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) adjudicated clinical events according to prespecified end point definitions. Adjudicated events included all-cause mortality, CV mortality, and HF hospitalization. In this post-hoc analysis, all-cause and CV mortality are the primary outcomes, with HF hospitalization a secondary outcome of interest.

At the time of PRECISION enrollment, each patient underwent a baseline 12-lead ECG. These tracings were centrally-adjudicated in a C5Research ECG core lab with QRS prolongation identified. LBBB and RBBB were coded according to standard definitions with QRS duration >120 ms. IVCD was defined a priori as QRS 101 to 120 ms regardless of morphology *or* QRS >120 ms not meeting classical BBB definitions. Given the lack of a published IVCD subclassification scheme, we further defined specific ECG criteria to dichotomize IVCD into those with LBBB-predominant (L-IVCD) and non-LBBB-predominant (O-IVCD) features. L-IVCD required *each* of the following ECG findings: (1) lead V1 net negative; (2) lead V1 without terminal positivity; and (3) lead I net positive. An example ECG schematic is included as Figure 1. In principle, delayed left ventricular activation is evident in net propagation anterior to posterior (lead V1 negative) and right to left (lead I positive). Patients with terminal V1 positivity were excluded, as late anterior activation away from the left ventricle is not consistent with predominant left His-Purkinje disease. In contrast, terminal rightward activation was permitted, provided net forces pulled leftward, to allow for delayed apical-septal or distal posteroseptal activation. We defined these criteria based on experience in the electrophysiology laboratory with bipolar endocardial activation mapping during sinus rhythm and ventricular arrhythmias.[20,21] These IVCD criteria were applied post hoc by study authors blinded to individual patient outcomes. Additionally, given the study definition of IVCD might include patients alternatively coded as incomplete LBBB or RBBB (QRS duration 101 to 120), IVCD groups were further dichotomized by QRS duration (101 to 120 versus >120).

Event rates are expressed in percentages for each of the QRS morphologies. Hazard ratios and corresponding 95% confidence intervals were generated using a Cox proportional hazards model with adjustment for stratification factors used in PRECISION randomization (arthritis type, aspirin use, and geographic region), as well as other clinically-relevant factors associated with mortality including age, gender, race, coronary artery disease (CAD), left ventricular hypertrophy (LVH), and diabetes mellitus (DM). Each prolonged QRS morphology (LBBB, RBBB, L-IVCD, and O-IVCD) was compared with narrow QRS (≤100 ms) as the reference group with p values calculated using log-rank tests. There were no adjustments for multiplicity. These analyses were performed for the composite PRECISION cohort and the individual subpopulations of established CVD and CVD at-risk. Kaplan-Meier curves were generated for the CV mortality end point. A 2-sided significance level of 0.05 was used for all comparisons. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

## Results

Of 24,081 patients studied in PRECISION, 22,607 (92%) had nonpaced, interpretable baseline ECGs. Overall, 21,367 (94.5%) had narrow QRS and 1,240 (5.6%) had prolonged QRS. In prolonged QRS patients, there were 766 RBBB (3.4%), 313 LBBB (1.4%), and 161 IVCD (0.7%). IVCD patients were subclassified into 95 L-IVCD (0.4%) and 66 O-IVCD (0.3%). The baseline clinical characteristics stratified by QRS classification can be found in Table 1. When comparing the CVD (n = 5,117 − 23%) and CVD-at-risk (n = 17,490 − 77%) populations, established CVD patients had higher rates of QRS prolongation across all categorizations except O-IVCD: any QRS prolongation (8.4% vs 4.6%), RBBB (5.2% vs 2.9%), LBBB (2.3% vs 1.1%), IVCD (1.0% vs 0.6%), and L-IVCD (0.7% vs 0.3%).

Adjudicated clinical outcome rates and unadjusted hazard ratios compared with narrow QRS patients are shown in Table 2A. In descending order, unadjusted all-cause

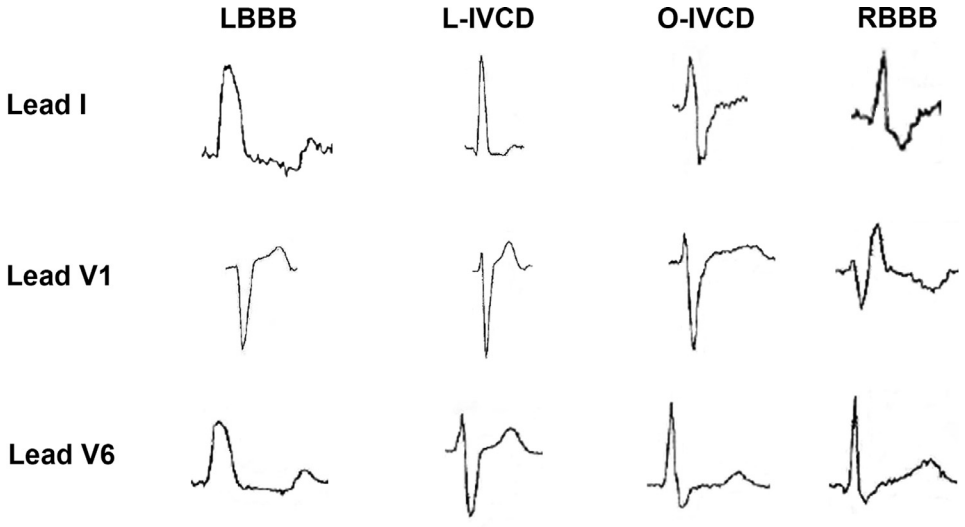


Figure 1. Schematic demonstrating example ECG morphologies in leads I, V1, and V6 for patients with LBBB, L-IVCD, O-IVCD, and RBBB classifications.

Table 1
Baseline clinical characteristics stratified by QRS classification

| Variable | Narrow (n = 21,367) | RBBB (n = 766) | LBBB (n = 313) | L-IVCD (n = 95) | O-IVCD (n = 66) | p Value* | p Value† |
|---|---|---|---|---|---|---|---|
| Age, mean (SD), years | 63 ± 9 | 68 ± 9 | 69 ± 8 | 66 ± 9 | 66 ± 11 | <0.001 | 0.090 |
| Female | 13869 (65%) | 335 (44%) | 210 (67%) | 35 (67%) | 35 (53%) | <0.001 | <0.001 |
| White | 15890 (74%) | 667 (87%) | 258 (82%) | 77 (81%) | 58 (88%) | <0.001 | 0.126 |
| BMI (kg/m$^2$) | 33 ± 7 | 33 ± 7 | 32 ± 6 | 34 ± 8 | 30 ± 5 | 0.021 | 0.007 |
| Primary prevention | 16682 (78%) | 500 (65%) | 196 (63%) | 61 (64%) | 51 (77%) | <0.001 | 0.158 |
| Arthritis | | | | | | 0.028 | 0.207 |
| Osteoarthritis | 19191 (90%) | 715 (93%) | 285 (91%) | 84 (88%) | 59 (89%) | | |
| Rheumatoid arthritis | 2176 (10%) | 51 (7%) | 28 (9%) | 11 (12%) | 7 (11%) | | |
| Diabetes m ellitus | 7530 (36%) | 307 (40%) | 97 (31%) | 38 (40%) | 21 (32%) | 0.021 | 0.026 |
| Hypertension | 16581 (78%) | 633 (83%) | 258 (83%) | 79 (84%) | 46 (70%) | 0.001 | 0.052 |
| Hyperlipidemia | 13318 (63%) | 536 (70%) | 205 (66%) | 69 (73%) | 45 (68%) | <0.001 | 0.382 |
| Current smoker | 4521 (21%) | 118 (16%) | 35 (11%) | 10 (11%) | 15 (23%) | <0.001 | 0.043 |
| Aspirin | 9647 (45%) | 450 (59%) | 196 (63%) | 53 (56%) | 42 (64%) | <0.001 | 0.489 |
| Statin | 11448 (54%) | 491 (64%) | 188 (60%) | 63 (66%) | 41 (62%) | <0.001 | 0.569 |
| ACE inhibitors/ARB | 8238 (39%) | 347 (45%) | 136 (44%) | 46 (48%) | 27 (41%) | <0.001 | 0.749 |
| Beta blockers | 6290 (29%) | 282 (37%) | 140 (45%) | 41 (43%) | 23 (35%) | <0.001 | 0.072 |

* Chi-square p value for across the 5 QRS classifications.
† Chi-square p value for across QRS classification after excluding the 'Narrow' group.

mortality was significantly increased in IVCD (6.9%, hazard ratio [HR] 3.9), LBBB (5.9%, HR 3.1), and RBBB (3.6%, HR 1.9) versus narrow (1.9%). For unadjusted CV mortality, only LBBB (4.3%, HR 4.4) and IVCD (3.6%, HR 3.6) remained significantly different (narrow 1.0%). Regarding HF hospitalization, only LBBB (4.5%, HR 8.0) differed from narrow.

When IVCD was subclassified, survival rates for L-IVCD were similar to LBBB, whereas O-IVCD most-resembled narrow QRS (Table 2B). L-IVCD (n = 95) had observed all-cause mortality of 10% (HR 6.0) and CV mortality 5.0% (HR 5.0), whereas O-IVCD had 1.8% for both all-cause and CV mortality (narrow 1.9% all-cause, 1.0% CV). Neither L-IVCD nor O-IVCD increased HF hospitalizations. Given

Table 2
Event rates and unadjusted hazard ratios for all-cause and cardiovascular mortality in the composite PRECISION cohort stratified by (A) traditional QRS classifications (RBBB, IVCD, LBBB) and (B) IVCD subclassification (L-IVCD vs O-IVCD). Population attributable risk for LVCD is calculated below

(A)

| Composite Cohort | Narrow (n = 21,367) | RBBB (n = 766) | IVCD (n = 161) | LBBB (n = 313) |
|---|---|---|---|---|
| All-cause mortality | 351 (1.6%) | 24 (3.1%) | 10 (6.2%) | 16 (5.1%) |
| Hazard ratio | | 1.9 (1.3−2.9) | 3.9 (2.1−7.3) | 3.1 (1.9−5.2) |
| p value | | 0.002 | <0.001 | <0.001 |
| Cardiovascular mortality | 187 (0.9%) | 12 (1.6%) | 5 (3.1%) | 12 (3.8%) |
| Hazard ratio | | 1.8 (1.0−3.2) | 3.6 (1.5−8.8) | 4.4 (2.5−7.9) |
| p value | | 0.05 | 0.002 | <0.001 |
| HF hospitalization | 106 (0.5%) | 7 (0.9%) | 1 (0.6%) | 12 (3.8%) |
| Hazard ratio | | 1.8 (0.9−4.0) | 1.3 (0.2−9.1) | 8.0 (4.4−14) |
| p value | | 0.11 | 0.81 | <0.001 |

(B)

| Composite Cohort | Narrow (n = 21,367) | O-IVCD (n = 66) | L-IVCD 100-120 ms (n = 58) | L-IVCD >120 ms (n = 37) | Total L-IVCD (n = 95) |
|---|---|---|---|---|---|
| All-cause mortality*** | 351 (1.6%) | 1 (1.5%) | 6 (10.3%) | 3 (8.1%) | 9 (9.5%) |
| Hazard ratio | | 0.9 (0.1−6.5) | 7.1 (3.2−15.8) | 4.7 (1.5−14.6) | 6.0 (3.1−12) |
| p value | | 0.93 | <0.001 | 0.003 | <0.001 |
| Cardiovascular mortality | 187 (0.9%) | 1 (1.5%) | 2 (3.4%) | 2 (5.4%) | 4 (4.2%) |
| Hazard ratio | | 1.7 (0.2−12) | 4.4 (1.1−17.7) | 5.9 (1.5−23.6) | 5.0 (1.9−14) |
| p value | | 0.59 | 0.02 | 0.005 | <0.001 |
| HF hospitalization | 106 (0.5%) | 0 (0%) | 0 (0%) | 1 (2.7%) | 1 (1.1%) |
| Hazard ratio | | – | – | 5.2 (0.7−37.2) | 2.2 (0.3−16) |
| p value | | 0.57 | 0.61 | 0.07 | 0.42 |

*** The incidence of all-cause mortality in LVCD (LBBB + L-IVCD) is 6.1% [(16 + 9)/(313 + 95)] versus 1.7% [(351 + 24+1)/(21,367 + 766+66)] in the absence of LVCD (narrow, RBBB, or O-IVCD). Thus, the population attributable risk of LVCD is 72% [(6.1 to 1.7)/6.1].

the potential for L-IVCD to include both incomplete LBBB (QRS duration 101 to 120 ms) and unequivocal IVCD (QRS duration >120 ms), unadjusted outcomes were further compared between QRS-stratified L-IVCD. Compared with narrow QRS, patients with L-IVCD and QRS duration 101 to 120 (n = 58) had significantly increased all-cause (12%, n = 6, HR 7.1 [3.2 to 16], p <0.001) and CV (4.3%, n = 2, HR 4.4 [1.1 to 18], p = 0.02) mortality. Similar mortality rates were observed in L-IVCD with QRS duration >120 ms (n = 37), both for all-cause (8.6%, n = 3, HR 4.7 [1.5 to 15], p = 0.003) and CV (6.0%, n = 2, HR 5.9 [1.5 to 24], p = 0.005) mortality, as well as a trend toward increased HF hospitalization (3.1%, n = 1, HR 5.2 [0.73 to 37], p=0.07).

After subdivision into established CVD and CVD-at risk, RBBB and O-IVCD patients experienced rates of all-cause mortality, CV mortality, and HF hospitalization similar to narrow QRS patients. For both the CVD-at-risk and established CVD populations, LBBB and L-IVCD exhibited higher overall outcome rates, albeit with heterogeneity observed. In CVD-at-risk, LBBB (n = 196) was associated with increased all-cause mortality (6.4%, HR 4.4 [2.4 to 8.0], p <0.001), CV mortality (5.1%, HR 7.0 [3.6 to 14], p <0.001), and HF hospitalization (4.0%, HR 11 [5.0 to 24], p <0.001). However, in established CVD and LBBB (n = 117), only HF hospitalization was increased (5.6%, HR 4.1 [1.6 to 10], p = 0.001). As for L-IVCD, in the CVD-at-risk population (n = 61), only all-cause mortality was significantly increased (11%, HR 8.5 [3.8 to 19], p <0.001), whereas in the established CVD population (n = 34), CV mortality was significantly increased (9.8%, HR 5.2 [1.6 to 16], p = 0.002) and all-cause mortality trended toward significance (9.8%, HR 2.9 [0.92 to 9.1], p = 0.06).

Multivariable Cox proportional hazards regression analysis was performed to generate adjusted hazard ratios for QRS prolongation categories compared with narrow QRS using 6 prespecified covariates and 3 randomization stratifiers. These adjusted HRs for all-cause and CV mortality can be found in Figure 2. LBBB and L-IVCD remain the only prolonged QRS classification groups strongly associated with increased all-cause and CV mortality. The adjusted HR for LBBB was 2.3 (1.4 to 3.8, p = 0.001) for all-cause and 3.6 (2.0 to 6.5, p <0.001) for CV mortality. The adjusted HR for L-IVCD was 4.0 (2.1 to 7.9, p <0.001) for all-cause and 3.6 (1.3 to 9.7, p = 0.001) for CV mortality. Given similar adjusted survival experiences for LBBB and L-IVCD, a composite LVCD variable was created requiring *either* LBBB or L-IVCD. The population attributable risk percentage for LVCD was calculated at 72% (Table 2). Thereafter, final Cox models predicting time to all-cause and CV mortality were created including LVCD and the prespecified confounders/stratifiers (Figure 3). For both all-cause and CV mortality, LVCD exhibited the strongest association with increased risk. The adjusted HR for LVCD was 2.8 (1.8 to 4.2, p <0.001) for all-cause mortality and 3.6 (2.2 to 6.1, p <0.001) for CV mortality. In contrast, the adjusted HR for other well-established risk factors were: CAD (all-cause: HR 1.7 [1.3 to 2.1], p <0.001; CV: HR 1.9 [1.3 to 2.6], p <0.001), LVH (all-cause: 1.4 [0.9 to 2.3], p = 0.16; CV: 1.6 [0.9 to 3.0], p = 0.13), DM (all-cause: 1.4 [1.1 to 1.7], p = 0.003; CV: 1.5 [1.1 to 2.0], p = 0.004). Cox survival curves displaying time to CV mortality stratified by QRS classifications and LVCD designation are shown in Figure 4**,** respectively. When the Cox regression was restricted to CVD at-risk, adjusted HRs were higher for all-cause 4.3 (2.6 to 7.0, p <0.001) and CV mortality 5.4 (2.8 to 11, p <0.001). For established CVD, LVCD remained significant for increased CV mortality at a HR of 2.5 (1.06 to 5.7, p = 0.03), though not for all-cause mortality (HR 1.6, 0.8 to 3.3, p = 0.20).

## Discussion

In this post-hoc analysis of 22,607 patients from the PRECISION trial, LVCD on baseline ECG was strongly associated with increased CV and all-cause mortality, even after adjusting for well-recognized CV risk factors. Increased mortality was independent of pre-existing CVD or whether LVCD was present in LBBB or L-IVCD form. Conversely, QRS prolongation in the absence of LVCD (RBBB and O-IVCD) conferred similar survival to narrow QRS.

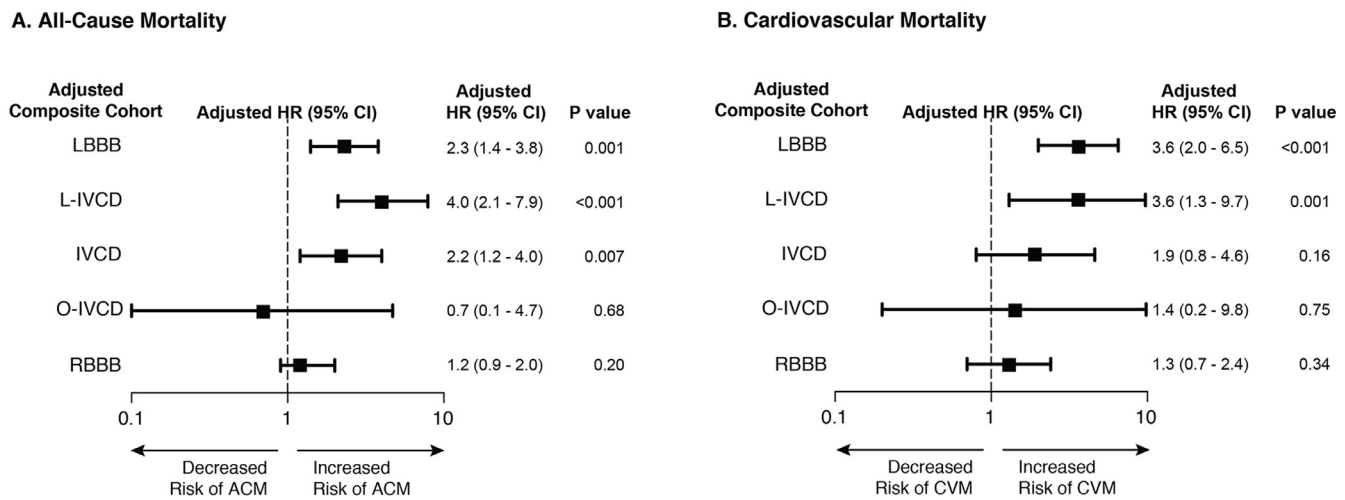


Figure 2. Forest plot depicting hazard ratios by QRS category for all-cause and cardiovascular mortality after adjustment for clinical covariates and randomization stratifiers.

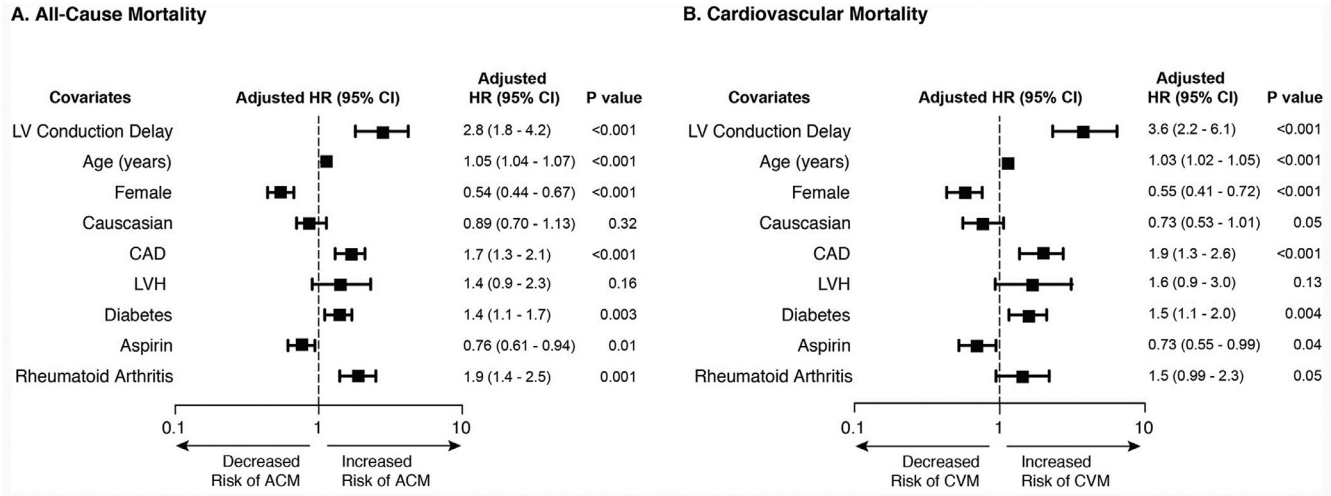


Figure 3. Forest plot depicting adjusted hazard ratios for all-cause and cardiovascular mortality using multi-variable, time-to-event Cox regression, identifying left ventricular (LV) conduction delay as the strongest included risk association.

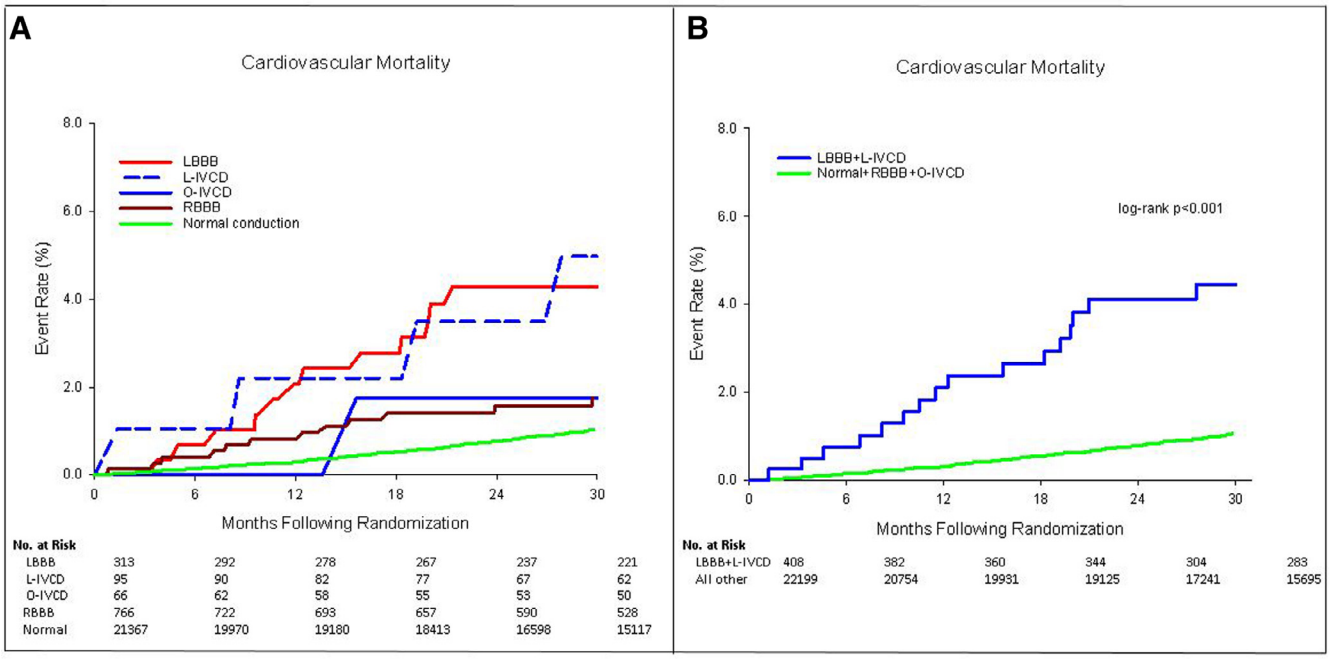


Figure 4. Cardiovascular mortality stratified by (*A*) QRS classifications with IVCD subclassified (L-IVCD vs O-IVCD) and (*B*) dichotomized by the presence or absence of left ventricular conduction delay (LBBB or L-IVCD).

The paucity of previous IVCD risk data may be attributable to a lack of standardized QRS definitions to identify disease states within the arborized His-Purkinje system. The most recent guideline statement[22] defines QRS prolongation >110 ms. However, the committee notes a 95 ms average that increases with age and male gender and varies with race.[23] As such, while complete BBB has a widely-applied thresholds of >120 ms, cutoffs for QRS prolongation, and by extension IVCD and incomplete BBB, vary routinely from 100 to 120 ms in previous studies.[4,5,24] In order to address these inconsistencies, we developed an IVCD classification scheme to dichotomize non-BBB QRS prolongation based on the presence (L-IVCD) or absence (O-IVCD) of delayed LV activation. QRS wavefront propagation was judged toward the left arm (lead I) and right precordium (lead V1), which is normally rapid without delayed anterior or rightward depolarization. From 100 to 120 ms, this approach consolidates incomplete BBB and IVCD starting at the lowest applicable threshold for QRS prolongation (100 ms). Above 120 ms, additional QRS morphology discrimination is provided by subdividing IVCD into L-IVCD and O-IVCD.

Application of these IVCD criteria provided excellent mortality stratification in the study population. L-IVCD survival was similar to LBBB, whereas O-IVCD outcomes mirrored RBBB and narrow QRS. The increase in mortality in the L-IVCD cohort persisted whether QRS duration was 100 to 120 or >120 ms, suggesting that the presence of

delayed LV activation, not necessarily the length, portends poorer survival. Only in HF hospitalization was LBBB associated with adverse prognosis, but not L-IVCD. However, L-IVCD >120 ms trended toward increased HF ($p = 0.07$), though the analysis was underpowered ($n = 37$).

The increase in adjusted mortality observed in patients with any LVCD raises the question whether targeted surveillance may be warranted for this under-recognized high-risk population, and if so, in what form. The adjusted HRs were *higher* in at-risk compared with established CVD patients (all-cause mortality 4.3 vs 1.6, CV mortality 5.4 vs 2.5). This disparity may reflect underdetection and undertreatment of clinically-silent, undiagnosed CV disease (atherosclerotic or structural), for which earlier screening and therapy may prove beneficial. Nevertheless, after adjusting for atherosclerotic disease, LVCD patients remained at increased risk of SCD. Indeed, 63% (10 of 16) of CV mortality in the LVCD population was attributable to SCD, with similar proportions seen in LBBB (58%, 7 of 12) and L-IVCD (75%, 3 of 4). These findings underscore the importance of an electrically intact left-sided His-Purkinje system. Perhaps a new "electrical dyssynchrony" parameter is needed in addition to well-recognized CV risk factors such as CAD, DM, and LVH. The identification and acknowledgment of LVCD as a unique disease state is a potentially practice-changing paradigm shift in how we conceptualize overall CV health and risk.

The current findings extend previous knowledge regarding left-sided dyssynchrony. In established HF patients with defibrillator (ICD) indications (ejection fraction [EF] <35%), LBBB is a well-established risk factor for worsening HF and CV mortality, a finding mitigated by cardiac resynchronization therapy (CRT).[6,7] In HF patients without ICD indications (EF 36% to 50%), LBBB portends higher all-cause mortality, worse EF decrement, and greater need for subsequent ICD.[8] These trends persist in iatrogenic LVCD through right ventricular pacing, whether with prepacing EF <40%,[25] 36% to 50%,[26] or preserved (>50%)[27] and at pacing burdens as low as 20%. Similarly, frequent premature ventricular contractions >24% burden, the majority of LVCD morphology, are associated with lower EF.[28] As observed in our study, previous work has shown increased SCD in LBBB patients,[9,10]. This is largely attributable to ventricular arrhythmias, though bradycardic death may also be higher, given progression to advanced atrioventricular block is more common in LBBB than RBBB.[17]

Although this post-hoc analysis was not randomized to QRS classification nor powered for subgroup analysis, the characteristics of the PRECISION trial were strongly favorable to retrospectively test a biologically plausible hypothesis. The population was large (22,607) and multinational (13 countries), adequately represented females (64%), and utilized clearly defined adjudicated outcomes over prolonged follow-up. Nevertheless, limitations remain. Given enrollment ECGs were obtained at 926 sites, there was likely lead placement variability that may have affected QRS classification. This cannot be practically controlled for, but the authors expect QRS misassignment to have occurred randomly and not act as a significant confounder. Furthermore, imaging data was not available for post-hoc review. As such, it is most appropriate to qualify *electrocardiographic* LVCD. Future imaging correlation is needed to determine if L-IVCD exhibits delayed *mechanical* activation compared with O-IVCD. Activation mapping of L-IVCD versus O-IVCD in the electrophysiology lab would provide further delineation to the sites and heterogeneity of left-sided conduction delay (His-Purkinje versus intramyocardial) in IVCD patients.

PRECISION recruited only patients with OA or RA, both populations (particularly RA) associated with increased CV risk.[29,30] Nevertheless, while RA was associated with increased mortality compared with OA in the study population, arthritis type did not differ across prolonged QRS classification and was adjusted for in multivariable analysis. Another limitation is small event numbers and subgroup underpowering, particularly within the L-IVCD classification. With larger populations, whether incident HF is significantly increased in L-IVCD patients with QRS >120 and a possible target for CRT could be more thoroughly explored. Most importantly, the proposed IVCD classification scheme requires external validation before clinical application.

## Conclusions

In conclusion, prolonged left ventricular conduction, whether in the form of LBBB or L-IVCD, is strongly associated with increased all-cause and CV mortality. The increased risk profile associated with LVCD persists across QRS durations (100-120 versus >120 ms) irrespective of established CVD.

## Disclosures

There are no pertinent relationships to report for any of the study authors.


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