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Association with Mortality and Heart Failure

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ACADEMIC DISSERTATION
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”*Muista, aamu koittaa aina”*

osastonylilääkäri Karri Aitola
yön päivystäjälle

To Tiia Haukipää,

the love of my life.

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Tampere, October 2021

Jani Rankinen

ABSTRACT

Cardiovascular (CV) and ischemic heart diseases are global burden of health and leading causes of death worldwide. In Finland, although their percentage of causes of death has decreased, they caused one third of all deaths in 2019. Heart failure is a worldwide epidemic with increasing prevalence as the population ages. The lifetime risk of heart failure for a person aged 55 years is 30 %. Identifying risk factors for heart failure is crucial, and early recognition of individuals at risk helps in the adaptation of preventive therapies.

The standard 12-lead resting electrocardiogram (ECG) provides valuable diagnostic and prognostic information on the heart, and many pathological changes seen in the ECG are associated with increased morbidity and mortality. High-risk of mortality and heart failure in individuals with intraventricular conduction delays (IVCDs) was first discovered over 100 years ago in the beginning of the 20th century, but several studies have presented conflicting results of their prognostic implications in general population.

The aim of this thesis was to elucidate and provide contemporary knowledge of long-term morbidity and mortality associated with intraventricular conduction blocks in the general population. We were especially interested in the risk of mortality and heart failure associated with these abnormal ECG findings.

This study was conducted as part of the Health 2000 survey, which consists of a nationally representative random sample of the Finnish population. The survey was carried out in 2000–2001 and consisted of 6 354 individuals (2 876 men and 3 478 women) aged 30 years or older who participated in a comprehensive health examination. The follow-up information of participants was available for over 15 years (median 15.9 years).

One of the main findings of this study was that the presence of traditional CV risk factors and CV diseases in predominantly middle-aged Finnish subjects with intraventricular conduction blocks do not vary from those in previously published data from the Western countries. Intraventricular blocks proved to have different prognostic implications depending on the type of IVCD. Within 10 years of the baseline health examination, 47 % of those with left bundle branch block (LBBB),

40 % of those with non-specific IVCD, and 37 % of those with right bundle branch block (RBBB) had died.

Throughout the over 15-year period of observation only 9 % of those with LBBB, 20 % of those with RBBB, and 24 % of those with non-specific IVCD remained free of any CV diseases. Non-specific IVCD, and LBBB by conventional criteria were associated with increased rate of CV mortality independently of several baseline variables. For LBBB, the risk of CV mortality was attenuated by the definition of the conduction delay, while non-specific IVCD carried the highest relative risk for CV and overall mortality.

During the observation, 49 % of the subjects with LBBB and 32 % of those with non-specific IVCD developed novel heart failure. Both blocks carried over three-fold risk of new-onset heart failure. The risk was independent of several CV risk factors and CV diseases, and even observed in individuals free of a known coronary heart disease. LBBB was also associated with incidence of a novel structural heart disease in over 15 years of observation, even after excluding those with prevalent ischemic heart disease and heart failure.

Throughout the observation, RBBB, left anterior and posterior fascicular blocks, and incomplete left and right bundle branch blocks were not independently related to excess mortality rates or risk of novel heart failure in the general population. Their prognosis was related to the presence or absence of classical CV risk factors and diseases.

Individuals with left ventricular hypertrophy (LVH) are vulnerable to congestive heart failure. In LVH, QRS duration carries valuable prognostic information. Even minor increases of QRS duration were related to a higher risk of CV mortality and novel heart failure, and the risk of both events increased with longer QRS duration independently of a prevalent ischemic heart disease. Even QRS duration within normal limits possesses a risk of new-onset heart failure in LVH as compared to those without LVH in the general population.

In conclusion, in a nationally representative population study of predominantly middle-aged subjects with a long-term follow-up, non-specific IVCD, LBBB by conventional criteria, and prolonged QRS duration in LVH carried excess risk of CV mortality and risk of new-onset heart failure. LBBB also carried a risk of novel structural heart disease. For RBBB and other blocks, the prognosis was related to the presence or absence of classical CV risk factors and existing CV diseases. These differences in prognostic implications of intraventricular blocks need to be taken into consideration in everyday clinical practice.

TIIVISTELMÄ

Sydän- ja verisuonitaudit sekä iskeemiset sydänsairaudet ovat maailmanlaajuisesti merkittävimmät terveysuhat sekä yleisimpiä kuolinsyitä. Vaikka niiden osuus kaikista kuolemansyistä on vähentynyt Suomessa, aiheuttivat ne edelleen kolmanneksen kuolemista vuonna 2019. Sydämen vajaatoiminta on maailmanlaajuinen epidemia, jonka esiintyvyys kasvaa jatkuvasti väestön ikääntyessä. Riski sairastua 55-vuotiaana loppuelämän aikana sydämen vajaatoimintaan on peräti 30 %. Sen estämiseksi on tärkeää tunnistaa sydämen vajaatoiminnan riskitekijät väestössä, ja hoitaa ne yksilötasolla mahdollisimman varhaisessa vaiheessa.

12-kytkentäinen levossa otettava sydänfilmi (EKG) tarjoaa tärkeää diagnostista ja ennusteeseen liittyvää tietoa sydämestä. Monet EKG:ssa todetut patologiset muutokset lisäävät kuolleisuutta ja sairastavuutta. Sydämen kammionsisäiset johtumishäiriöt liitettiin sydämen vajaatoimintaan ja korkeaan kuolleisuuteen jo yli 100 vuotta sitten 1900-luvun alussa, mutta näyttö niiden merkityksestä väestötasolla on ristiriitaista.

Tämän tutkimuksen tavoitteena oli kerätä nykyaikaista tietoa kammionsisäisten johtumishäiriöiden pitkäaikaisennusteesta ja niihin liittyvästä sairastavuudesta. Erityisenä mielenkiinnon kohteena oli selvittää, liittyykö näihin johtumishäiriöihin kohonnutta kuolleisuutta tai riskiä sairastua sydämen vajaatoimintaan seurannassa.

Tutkimus toteutettiin osana Suomessa satunnaisotannalla tehtyä Terveys 2000 väestötutkimusta. Tutkimukseen osallistui 6 354 yli 30-vuotiasta henkilöä (2 876 miestä ja 3 478 naista) vuosina 2000–2001. Suurin osa heistä oli keski-ikäisiä. Tutkittavat osallistuivat kattavaan terveystarkastukseen, ja heitä seurattiin yli 15 vuoden ajan (mediaani 15,9 vuotta) terveystarkastuksesta.

Havaitsimme, että EKG:ssa havaittuihin kammionsisäisiin johtumishäiriöihin liittyy runsaasti sydän- ja verisuonisairauksia sekä niiden riskitekijöitä. Tuloksemme olivat yhtenevät aiemmin länsimaissa julkaistujen tulosten kanssa. Kammionsisäisen johtumishäiriön ennusteen havaittiin olevan riippuvainen johtumishäiriön tyypistä. Jo 10 vuoden seurannan aikana 47 % tutkittavista, joilla havaittiin vasen haarakatkos (LBBB), 40 % tutkittavista, joilla havaittiin epäspesifi kammionsisäinen johtumishäiriö (IVCD), ja 37 % tutkittavista, joilla havaittiin oikea haarakatkos (RBBB) olivat menehtyneet.

Koko 15 vuoden seurannan aikana vain 9 % tutkittavista, joilla havaittiin LBBB, 20 % tutkittavista, joilla havaittiin RBBB, ja 24 % tutkittavista, joilla havaittiin IVCD ei sairastunut sydän- ja verisuonitauteihin. Korkein suhteellinen sydän- ja verisuonitautikuolleisuus oli tutkittavilla, joilla EKG:ssa havaittiin IVCD tai LBBB. LBBB:n merkitys riskitekijänä sydän- ja verisuonitautikuolleisuudelle havaittiin olevan riippuvainen johtumishäiriön tarkemmasta määritelmästä. IVCD assosioitui ainoana johtumishäiriönä itsenäisenä riskitekijänä kokonaiskuolleisuudelle ja siihen liittyvä riski sydän- ja verisuonitautikuolleisuuteen oli suhteellisesti korkein kaikista kammionsisäistä johtumishäiriöistä.

Seurannan aikana 49 % tutkittavista, joilla havaittiin LBBB, ja 32 % tutkittavista, joilla havaittiin IVCD sairastuivat sydämen vajaatoimintaan. Sairaus ei ollut heillä aiemmin tiedossa. Molemmat johtumishäiriöt lisäsivät riskiä sairastua sydämen vajaatoimintaan yli kolminkertaiseksi, ja riski sairastua sydämen vajaatoimintaan havaittiin myös tutkittavilla, joilla ei ollut tiedossa olevaa iskeemistä sydänsairautta. LBBB:n havaittiin myös lisäävän riskiä sairastua rakenteelliseen sydänsairauteen yli 15 vuoden seurannan aikana. Riski havaittiin myös tutkittavilla, joilla ei ollut terveystarkastuksessa viitteitä sydämen vajaatoiminnasta tai sepelvaltimotaudista.

Koko seurannan aikana oikea haarakatkos, haarakekatkokset tai osittaiset haarakatkokset eivät lisänneet riskiä sairastua sydämen vajaatoimintaan eikä kyseisillä tutkittavilla havaittu olevan korkeampaa kuolleisuutta, kun otettiin huomioon samanaikaiset sydän- ja verisuonitaudit sekä niille altistavat riskitekijät.

Sydämen vasemman kammion paksuuntuminen eli kammiohypertrofia on merkittävä riskitekijä sydämen vajaatoiminnalle. Sydämen sähköisen aktivaation leviämiseen sen rakenteissa kuluvan ajan eli QRS keston havaittiin välittävän tärkeää tietoa kammiohypertrofiassa. Pienikin QRS keston pidentyminen assosioitui korkeampaan kuolleisuuteen ja riskiin sairastua sydämen vajaatoimintaan tutkittavilla, joilla havaittiin kammiohypertrofia, riippumatta samanaikaisesta iskeemisestä sydänsairaudesta. Havaitsimme, että kammiohypertrofia itsessään myös QRS kestosta riippumatta lisäsi riskiä sairastua sydämen vajaatoimintaan, mutta riski korostui voimakkaasti QRS keston pidentyessä.

Yhteenvetona todetaan, että LBBB, IVCD ja QRS keston pidentyminen kammiohypertrofiassa liittyivät korkeampaan sydän- ja verisuonitautikuolleisuuteen sekä riskiin sairastua sydämen vajaatoimintaan väestötasolla. LBBB:n havaittiin myös lisäävän riskiä sairastua rakenteelliseen sydänsairauteen. Sen sijaan RBBB:n ja muiden kammionsisäisten johtumishäiriöiden ennusteen havaittiin liittyvän enemmänkin samanaikaisiin sydän- ja verisuonitauteihin sekä niiden riskitekijöihin.

CONTENTS

ABBREVIATIONS

AV	Atrioventricular
BMI	Body Mass Index
CHD	Coronary Heart Disease
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
ECG	Electrocardiogram
HDL	High-density Lipoprotein
HR	Hazard Ratio
HV	His-Ventricular
ICD	International Classification of Diseases
iLBBB	Incomplete Left Bundle Branch Block
iRBBB	Incomplete Right Bundle Branch Block
IVCD	Intraventricular Conduction Delay
LAFB	Left Anterior Fascicular Block
LBBB	Left Bundle Branch Block
LDL	Low-density Lipoprotein
LPFB	Left Posterior Fascicular Block
LSFB	Left Septal Fascicular Block
LVH	Left Ventricular Hypertrophy
MC	Minnesota Definition
RBBB	Right Bundle Branch Block
R-R' pattern	R' amplitude ≤ R in either of leads V1 and V2
SD	Standard Deviation

ORIGINAL PUBLICATIONS

Publication I Rankinen J, Haataja P, Lyytikäinen L-P, Huhtala H, Lehtimäki T, Kähönen M, Eskola M, Pérez-Riera A, Jula A, Rissanen H, Nikus K, Hernesniemi J. Long-term outcome of intraventricular conduction delays in the general population. Annals of Noninvasive Electrocardiology. 2021; 26(1):e12788.

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Manuscript III Rankinen J, Haataja P, Lyytikäinen L-P, Huhtala H, Lehtimäki T, Kähönen M, Eskola M, Tuohinen S, Pérez-Riera A, Jula A, Rissanen H, Nikus K, Hernesniemi J. Prevalence and Long-term Prognostic Implications of Prolonged QRS Duration associated with Left Ventricular Hypertrophy in the General Population. 2021. *Submitted.*

AUTHOR CONTRIBUTIONS

Publication I The study was designed by J. Rankinen, P. Haataja and K. Nikus. J. Rankinen performed the analyses and wrote the original manuscript. The project was supervised by K. Nikus, and all the authors provided critical feedback and helped shape the manuscript.

Publication II J. Rankinen conceived of the original idea, performed the analyses, and wrote the original manuscript. The project was supervised by K. Nikus, and all the authors provided critical feedback and helped shape the manuscript.

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1 INTRODUCTION

Cardiovascular (CV) and ischemic heart diseases are global burden of health and leading causes of death worldwide (World Health Organization 2020). In Finland, although their share causes of death has decreased, they caused one third of all deaths in 2019 (Statistics Finland 2020). Heart failure is a worldwide epidemic with increasing prevalence as the population ages. The lifetime risk of heart failure for a person aged 55 years is 30 % (Ponikowski et al. 2016). Identifying risk factors for heart failure is crucial, and early recognition of individuals at risk helps in the adaptation of preventive therapies.

The 12-lead resting electrocardiogram (ECG) is a standard tool in the CV risk assessment in both clinical practice and urgent situations. The presence of a bundle branch block provides valuable prognostic information, but also aggravates the interpretation of the ECG. After the first experimental bundle branch block was produced in 1909 (Eppinger and Rothberger 1909), it was realized that while subjects with wide and bizarre QRS complex could live probably years after its first presence, the ECG pattern was frequently associated with heart failure and high mortality due to pump failure (Carter 1914). A few years later, the clinical significance of a peripheral block beyond main the branches of the conduction system was explored and was related to high mortality rates (Oppenheimer and Rothschild 1917).

The Framingham Heart Study was a pioneer epidemiological study and remains the most famous and influential investigation in CV disease epidemiology. The study established a close relation to CV diseases associated with bundle branch blocks in late 1970s (Schneider et al. 1979, 1980). Alarmingly, only 11 % of subjects with left bundle branch block (LBBB) remained free of CV diseases in the observation and 50 % died within 10 years of the onset of LBBB. Interestingly, at the same time other investigators did not link neither LBBB nor right bundle branch block (RBBB) to excess mortality (Rodstein et al. 1951, Rotman and Triebwasser 1975).

In 1968, Rosenbaum and his colleagues elucidated clinicians of the existence and clinical significance of *hemiblocks* (Rosenbaum et al. 1968), satisfying the needs of every cardiologist. But the original observation of intraventricular blocks of the divisions of the left infra-Hisian conduction pathways and incomplete bundle branch

blocks originated from the canine studies of Rothberger and Winterberg over one hundred years ago (Rothberger and Winterberg 1917). Rosenbaum observed that a block in the left posterior fascicle (LPFB) is most often seen in combination of RBBB and is a precursor of a complete heart block, eventually requiring a cardiac pacemaker.

Even in the modern era of cardiology in the 21st century, the presence of bundle branch blocks and hemiblocks in the ECG provides invaluable, though occasionally tragic information of the heart in urgent situations. LBBB hampers the diagnosis of acute myocardial infarction, while the onset of a new RBBB, often with concomitant left anterior fascicular block (LAFB), is a strong indicator of occlusion of the left anterior descending artery, or even left main, requiring emergent coronary angiography and percutaneous coronary intervention in context of persistent ischemic symptoms (Ibanez et al. 2018). Nevertheless the modern treatment of these patients, the prognosis of patients with bundle branch blocks in the setting of acute myocardial infarction remains poor.

In late 1960s it was found out that the mortality associated with ECG evidence of left ventricular hypertrophy (LVH) was critically high – in a cohort of men 45 years of age or older the probability of dying within eight years of the first appearance of this pattern was more than a half. In fact, mortality was greater in persons with ECG-LVH than in persons surviving acute myocardial infarction (Kannel et al. 1969).

The Framingham Heart Study researchers found LVH to be strikingly related to blood pressure (Kannel et al. 1972), and identified hypertension as the cardinal precursor for congestive heart failure in early 1970s. The study also related the natural history of congestive heart failure to very grave prognosis – more than half of the subjects were dead within five years after the incidence of heart failure (McKee et al. 1971). Despite remarkable improvements in medical therapy towards the end of the 20th century (Captopril Multicenter Research Group 1983, Swedberg and Kjekshus 1987, Yusuf et al. 1992), the prognosis of heart failure remained miserable (Owan et al. 2006). In the early 21st century, several randomized trials demonstrated benefits of cardiac resynchronization therapy (CRT) on patients with heart failure with impaired systolic pump function and wide QRS in the ECG. Later, it was found out that the effect of CRT is highly dependent on the type of the conduction delay (Zareba et al. 2011, Cunnington et al. 2015). The correct ECG diagnosis of a bundle branch block appeared to be more crucial than ever.

At the same time, several population studies were conducted to explore associations between bundle branch blocks and mortality – with conflicting results

(Bussink et al. 2013, Zhang et al. 2016). Most of these studies focused only on selected intraventricular blocks (Eriksson et al. 2005, Mandyam et al. 2013, Zhang et al. 2013, Mentz et al. 2015). Some authors showed that RBBB was associated with increased mortality (Bussink et al. 2013), while other investigators found no effect on outcome (Haataja et al. 2015). Studies evaluating the prognostic impact of LBBB on mortality are also somewhat conflicting (Schneider et al. 1979, Imanishi et al. 2006, Haataja et al. 2015), and even the standard ECG criteria for LBBB was challenged 10 years ago (Strauss et al. 2011). There is no population-based data whether the definition of LBBB affects the prognosis.

Studies conducted in recent years have evaluated the role of LBBB inducing left ventricular functional decline (Vaillant et al. 2013, Sze et al. 2017, Nazif et al. 2019), while RBBB should play no significant negative role in this aspect (Bussink et al. 2013). Structural heart diseases with the potential for an inferior outcome have been associated with the presence of intraventricular conduction delays (IVCDs) (Dec and Fuster 1994), but no prior study has evaluated the predictive value of IVCDs as risk markers for a novel structural heart disease in a general population. Study data regarding the prognostic implications of fascicular blocks, incomplete bundle branch blocks and the R-R' pattern on mortality and novel heart failure is scarce. Most studies do not differentiate R-R' pattern from incomplete RBBB (iRBBB) pattern. Only a few prior population studies have assessed the clinical significance of incomplete LBBB (iLBBB) and found no relation to CV mortality (Tervahauta et al. 1996, Haataja et al. 2015).

Assessment of LVH in the standard 12-lead ECG is recommended for every hypertensive individual (Williams et al. 2018, Unger et al. 2020) and ECG-LVH is predictive of future CV events independently of echocardiography findings (Williams et al. 2018). The principal findings in LVH are increases of QRS amplitude and duration, and abnormalities of ST-segment with T-wave changes (Hancock et al. 2009). Previous studies have been dedicated to the prognostic relevance of different voltage criteria-based definitions for LVH (Paolo et al. 1998, Hsieh et al. 2005, Cuspidi et al. 2014, Porthan et al. 2015), but the prevalence and prognostic significance of QRS duration in ECG-LVH has not been well established in general population.

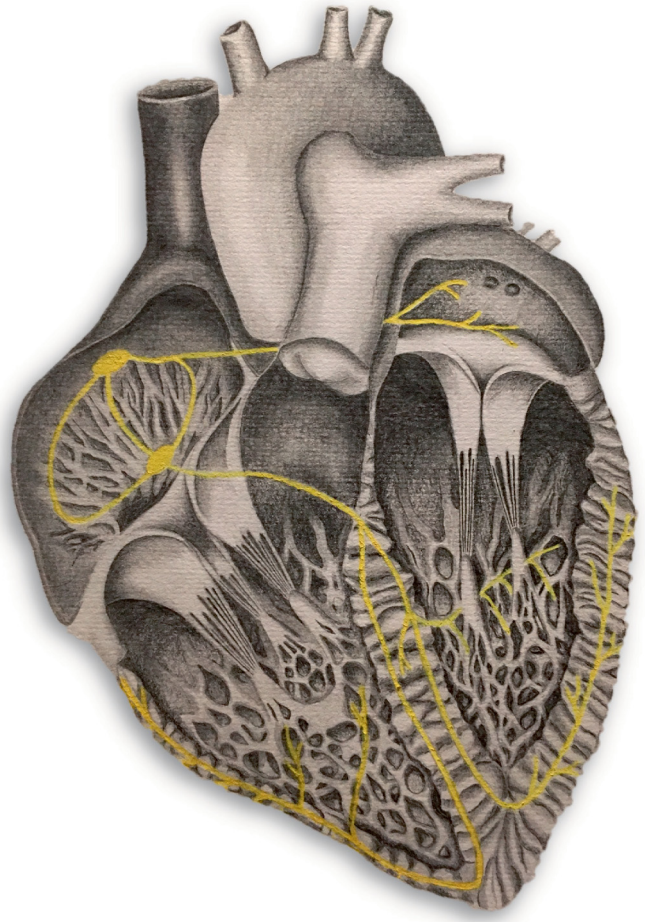
Therefore, the focus of this thesis was to provide contemporary knowledge regarding the prognostic significance of intraventricular conduction blocks in the standard 12-lead resting ECG and study the long-term association between IVCDs and CV and all-cause mortality, novel heart failure and structural heart disease among a Finnish general population aged 30 years or more.

2 REVIEW OF THE LITERATURE

2.1 The Cardiac Conduction System

The cardiac conduction system ensures that the signal originating from the sinoatrial node of the right atrium is propagated throughout the atrial and ventricular myocardium to ensure a synchronized and timely contraction of the heart muscle. In 1839, Jan Evangelista Purkinje discovered a net of fibers in the ventricular subendocardium of a sheep heart (Willius and Dry 1948), later to be named *Purkinje fibers* though their physiological properties were not understood before the 20th century (Tawara 1906). After the remarkable discovery of these distal intraventricular fibers of the conduction system, Walter Gaskell described in the early 1880s that the impulse originated from the atrium slows at the junctional fibers between atrial and ventricular chambers (Gaskell 1883). Gaskell demonstrated that cutting these fibers caused a "block" and with increasing cuts the ventricle responded only to second, then third etc. beat of the atrium. With a complete transsection the ventricle stopped completely, only to begin beating again at a slower rate and independent of the atrium (Silverman et al. 2006), producing a third degree or complete atrioventricular (AV) block though the AV bundle itself had yet to be discovered. Gaskell's findings provided the essential framework for the discovery of the bundle of His by Dr. Wilhelm His Jr. in 1893 (His 1893, Silverman et al. 2006). In 1904, Retzer and Braeunig described independently of each other the two distinct branches of the conduction system: the left and the right bundle branches (Tawara 1906). In 1906, Sunao Tawara discovered the AV bundle and realized that the network of fibers form an electrical pathway throughout the heart muscle. Dr. Tawara named the network as the "atrioventricular connecting system" (Tawara 1906) and that it originated from the AV node, penetrated the fibrocartilaginous portion of the septum at the bundle of His, then dividing into left and right bundle branches and downward to reach the terminal ramifications of the Purkinje fibers (Silverman et al. 2006) (Figure 1). In honor of his work, the AV bundle was called as the node of Tawara for more than 50 years. Finally, the origin of the electrical impulse was tracked down by Keith and Flack to the junction of the superior vena cava and right atrium (Keith and Flack 1907), the sinoatrial node, in 1907.

Figure 1. The Conduction System of the Heart.



Anatomically, the bundle of His composes of two segments: penetrating and branching portions. Arising from the AV node, the penetrating portion of the His bundle passes through the annulus fibrosus and runs underneath the membranous septum before going through the central fibrous body close to the mitral ring and the septal leaflet of the tricuspid valve. The branching portion of the bundle of His extends from the point where the bundle begins giving the most posterior fibers (the first fibers of the left bundle branch) to the point which marks both the most anterior strands of the left bundle branch (the last fibers) and the very beginning of the right bundle branch. As such, there is no true bifurcation of the main bundle, and this

particular point has been named "pseudobifurcation". The branching segment from which the left main bundle branch emerges lies at the inferior border of the membranous septum between the non-coronary and right coronary cusps of the aortic valve (Elizari 2017).

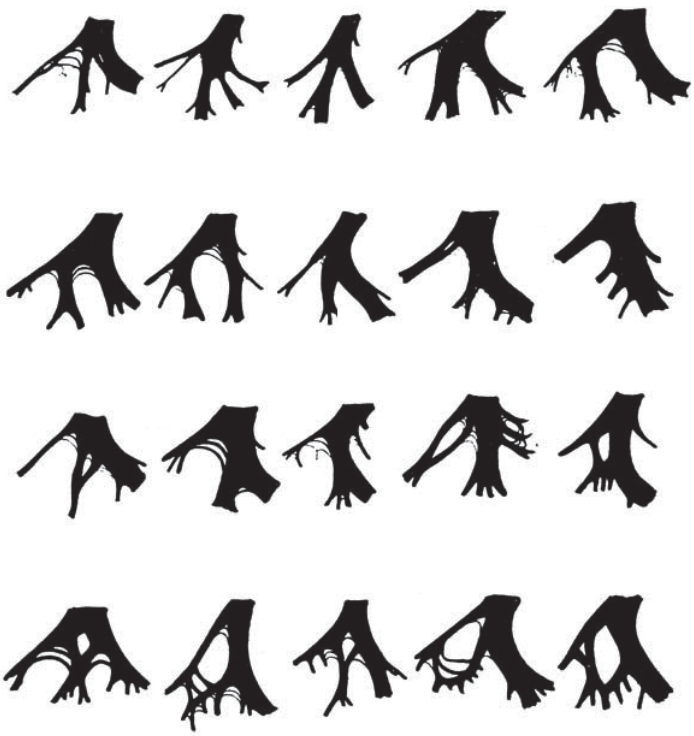
In Vienna in 1909, Eppinger and Rothberger created the first experimental bundle branch block when they injected silver nitrate into canine ventricular muscle (Eppinger and Rothberger 1909). They observed that injection to intraventricular septum produced marked ECG alterations that they believed were due to injury of the major branches of the cardiac conduction system, confirming the statement with clinical cases in the following year (Eppinger 1910). Ironically, this remarkable discovery led to 20-year confusion of the pattern of the LBBB, which was mistakenly diagnosed as RBBB due to anatomical differences of the heart between dogs and humans (Wilson 1942, Flowers 1987). In 1914, Carter published ECG series of several patients with bundle branch blocks and the noted an association with heart enlargement and failure (Carter 1914). Carter described the original criteria for the pattern of bundle branch block but continued to switch the diagnosis of RBBB and LBBB. It was not until the work of Oppenheimer and Pardee in 1920 and Barker in 1930 when they proposed that the diagnosis of LBBB and RBBB had been reversed and the debate was finally settled (Oppenheimer and Pardee 1920, Barker et al. 1930).

While the universal concept of left anterior or posterior fascicular block had neither been developed and accepted at that time, German researchers Rothberger and Winterberg reported in 1917 that cutting canine left anterior fibers reduced the R waves and deepened the S waves in the ano-esophageal lead, whereas posterior cuts did the opposite (Rothberger and Winterberg 1917). This pioneer study was many years ahead of its time, and it took approximately 50 years before the universal agreement of the concepts of the blocks in the finer branches of the left conduction stem (Uhley 1979). In 1934, Wilson gave serious consideration to the possibility that the deep S waves in leads II and III were due to a lesion of the anterior division of the left bundle branch (Wilson et al. 1934, Uhley 1979). Later, in 1957 Grant stressed that the marked left axis deviation might be caused by the block of the anterior fibers of the left bundle branch (Grant 1958).

In 1968, Rosenbaum and his colleagues provided detailed knowledge of the trifascicular nature of the cardiac conduction system in their famous reviews *Los Hemibloqueos* (Rosenbaum et al. 1968), and *The Hemiblocks* (Rosenbaum 1970) in 1970. The authors showed that the left bundle branch consisted of two divisions and the concept of hemiblock was born. However, as early as 1906, Dr. Tawara (Tawara 1906) described the trunk of the left bundle branch splits actually into three fascicles

instead of two: anterior, posterior and septal (Figure 1). The septal fibers are given off by the left main truncus, the posterior division, or less frequently by anterior division, or both (Rosenbaum et al. 1968, Rosenbaum 1970, Demoulin and Kulbertus 1972, Elizari et al. 2007) (Figure 2). These three fascicles interconnect as a fan-like network (Demoulin and Kulbertus 1972) carrying the cardiac impulse into both left and right ventricle and to the distal Purkinje (Robinson 1929) network.

Figure 2. The Left Infra-Hisian Conduction System. The left anterior fascicle is on the viewer's left. In most examples, the middle septal fibers arise from the left main truncus (sketches on the top), from the anterior fascicle (2nd row), from the posterior fascicle (3rd row), or from both fascicles, interconnecting as a fan-like network. From the original work of Demoulin and Kulbertus (Demoulin and Kulbertus 1972).



Term "bifascicular block" is referred when there is a concomitant block in two fascicles, most commonly in form of RBBB with LAFB though some authors classify LBBB as a bifascicular block. When there is a fixed block of one fascicle with intermittent failure of each fascicle, or a fixed block in two fascicles (bifascicular block) with evidence of 2nd degree AV block, term "incomplete trifascicular block"

can be applied. Some authors also classify a fixed bifascicular block with 1st degree AV block as incomplete trifascicular block. However, 1st degree AV block is a misnomer, and no true block is present as each P wave is conducted but with a prolonged PR interval >200 ms. Trifascicular block is complete if all the fascicles have completely failed – that is, a complete 3rd degree AV block with an escape rhythm with features of bifascicular block. Though the guidelines of the American College of Cardiology and the American Heart Association (Surawicz et al. 2009) do not recommend use of terms bifascicular or trifascicular block and counsels instead describing the each conduction block separately, terms bifascicular and trifascicular block are frequently referred in the literature and in everyday clinical practice.

2.2 Etiology of Bundle Branch Blocks and the Natural Course of High-Grade AV Block

The majority of the conduction delays are secondary to different processes affecting any of the bundle branches or fascicles. In addition to increasing age (particularly over 50 years), male sex, hypertension, heart enlargement, heart failure, coronary heart disease (CHD), and diabetes have been established as predictors of incident bundle branch block in general population (Schneider et al. 1980, Eriksson et al. 2005, Bussink et al. 2013, Yiheng et al. 2016).

In Latin America, Chagas cardiomyopathy is an important cause of bundle branch blocks. The etiologic agent is protozoan Trypanosoma cruzi, typically endemic in Central and South America but immigration patterns have resulted in large numbers of infected individuals in formerly nonaffected areas including Europe and United States, with at least 300 000 infected individuals in North America alone. Infection persists for lifetime and is responsible for 7.5 times as many disability-adjusted life-years lost as malaria, causing serious cardiac disease in ⅓ of those infected, progressing from conduction disturbances (typically RBBB with or without LAFB) and AV blocks to dilated cardiomyopathy with heart failure, ventricular arrhythmias, stroke, and other systemic or pulmonary embolisms (Rosenbaum 1964, Nunes et al. 2018).

Rosenbaum suggested that patients with the primary degenerative disease of the cardiac conduction system could be further subcategorized into those with Lenègre's disease and Lev's disease (Rosenbaum 1970). Electrocardiographically, both Lenègre and Lev disease are characterized by chronic conduction delay through the His-Purkinje system, resulting in varying degrees of AV block and bundle branch block.

Lev's disease (Lev 1964a) is characterized by senile sclerosis and calcification of the left side of the cardiac skeleton with secondary involvement of the conduction system with the aging of the heart, first seen at the fourth decade. These structures include central fibrous body, pars membranacea, aortic sinuses, ventricular septum and mitral annulus, and the conduction system is primary involved at the bundle of His and the bifurcation of proximal bundle branches. By the sixth and seventh decade, the majority of the hearts show these changes (Lev 1964b), occasionally progressing to advanced trifascicular block. Hypertension accelerates the process (Rosenbaum 1969). Lev's disease is the most frequent cause of chronic bifascicular block in elderly people without apparent organic heart disease who eventually develop complete heart block (Rosenbaum 1968, Elizari et al. 2007), and is perhaps the most common cause of permanent AV block (Lev 1964b).

Lenègre's disease (Lenegre 1964) is characterized by bilateral fibrosclerotic degeneration of the distal His-Purkinje system, limited to the conduction system. Hereditary Lenègre disease is a genetic defect of the Na^+ ion channel gene *SCN5A* (Schott et al. 1999) that exacerbates the natural age-related progressive alteration in cardiac conduction velocity (Probst et al. 2003). The same gene is associated with other cardiac entities, such as Brugada syndrome and long QT syndrome 3 (Park and Fishman 2011). In Lenègre's disease, chronic cardiac conduction defect progressively develops in relation to age, leading to complete heart block.

The first known report of Stokes-Adams attack with ECG recordings of high-grade AV block was described by van den Heuvel in 1908 (van den Heuvel 1908), though the link of recurring fainting episodes accompanied with slow heart rate was observed by both Adams in 1827 (Adams 1827) and Stokes in 1846 (Stokes 1846), and Gerbezius (Gerbezius 1717) and Morgagni (Morgagni 1761) as early as in the 18th century. The etiologic factor for complete heart block is most often idiopathic fibrosis in absence of significant cardiac disease. In a Finnish study (n = 6 146) (Kerola et al. 2019) AV block (2nd or 3rd degree AV block; n = 58) was not preceded by acute coronary syndrome or coronary revascularization procedure in 69.0 % of the subjects. Previous studies have associated male sex, older age, myocardial infarction, heart failure, high systolic blood pressure and high fasting glucose level, alongside with certain ECG parameters of conduction disorder (prolonged PR interval, RBBB and LBBB, and prolonged QRS duration) with incidence of eventual complete AV block and/or pacemaker implantation (Eriksson et al. 2005, Cheng et al. 2009, 2010, Bussink et al. 2013, Kerola et al. 2019, Rasmussen et al. 2019). In the Finnish study, elevated systolic blood pressure was associated with increased risk of AV block even after adjustment for baseline and incident major coronary events

during the follow-up extending to 32 years. Of note, restricting the outcome to 3rd degree AV block alone had no meaningful change in observations, and it was estimated that almost half of the AV blocks could be connected to an elevated systolic blood pressure (Kerola et al. 2019). Other causes for advanced AV block include inflammatory and infiltrative myocardial diseases (such as cardiac sarcoidosis and giant cell myocarditis), and infectious myocardial diseases (including Lyme disease, Chagas disease as described earlier, and viral myocarditis). In the 21st century, transcatheter aortic valve implantation has emerged as a valid alternative to traditional surgical aortic valve replacement in patients with severe aortic stenosis but high surgical risk, leading to increased iatrogenic causes for LBBB and complete heart block related to the close proximity of the AV conduction system to the aortic valvular complex (Siontis et al. 2014).

Rosenbaum suggested that 5 – 10 % of the patients with chronic bundle branch block in general population develop complete heart block over many years (Rosenbaum 1970). This rate is in line with other epidemiological studies which have estimated the risk approximately 5 – 15 % over 30 years of observation (Schneider et al. 1980, Eriksson et al. 1998, 2005, Bussink et al. 2013). The risk is pronounced in those with a bifascicular block (Rosenbaum et al. 1968, Rosenbaum 1970). In clinical cases of sequential failure of the conduction fibers leading to complete AV block, LAFB preceded RBBB and the additional involvement of the left bundle branch or its posterior division led to a complete heart block (Elizari et al. 2007).

From early 1970s to 1980s the natural course of the primary conduction disease was investigated. Early studies reported that 16 – 26 % of individuals with chronic bifascicular block, typically in their early 60s, have no apparent CV disease and were classified as having a primary conduction disease (Scanlon et al. 1970, Dhingra et al. 1979b, McAnulty et al. 1982). Spontaneous high-grade AV block developed in 1 % of these patients (n = 82) compared to 5 % in those with organic heart disease during the mean follow-up of 3.5 years (Dhingra et al. 1979b), though Scanlon et al. (Scanlon et al. 1970) reported a higher incidence (24 %) of spontaneous AV block in patients without apparent organic heart disease (n = 25) during the average follow up of 2 years and the complete heart block developed over several years in some of the patients. However, the risk of death due to CV causes was low (4 – 12 %) in patients with primary conduction disease.

In a prospective study of 554 patients with chronic bifascicular or trifascicular conduction disease (McAnulty et al. 1982), the rate of complete heart block was 1.0 % per year – similar to the earlier work (Dhingra et al. 1979a) of 452 patients with 2.0 % rate of spontaneous complete heart block. During the average follow up

of 3.5 years, 28.9 % of the patients died – of these 42 % were sudden, 18 % of these were due to probable tachyarrhythmia and only 3 % were due to documented bradyarrhythmia though in 24 % of the patients the cause of sudden death was unknown. A prolonged PR interval (13 % of all patients) was associated with increased chance of death, but there was no significant difference in the incidence of documented complete heart block between those with a normal or prolonged PR interval. At five years, the overall mortality was 29 % and 49 % in patients with primary conduction disease and CHD, respectively.

The conduction time from the His bundle to the onset of the QRS complex is referred as the HV interval (Alpert and Flaker 1984). In a prospective study of 517 patients with chronic bifascicular block (Dhingra et al. 1981), 39 % of the patients had a prolonged HV interval (>55 ms) – 24 % of these had primary conduction disease. The cumulative incidence of spontaneous AV block was 10 % in the normal and 20 % in the prolonged HV group at 7 years. CV mortality and sudden death were more common in patients with a prolonged HV interval. In another study from 1980s with 313 patients (Scheinman et al. 1982), spontaneous AV block during the mean follow up of 3.4 years was more common in patients with HV interval >70 ms (12 %) and extremely high (24 %) in patients with HV interval >100 ms. Thus, the recent guidelines of the European Society of Cardiology and the American College of Cardiology and the American Heart Association recommend implanting a pacemaker in patients with unexplained syncope and chronic bifascicular block in the presence of HV interval ≥70 ms (Brignole et al. 2018, Kusumoto et al. 2018).

Syncope in patients with bifascicular block could potentially be a manifestation of intermittent complete heart block. In a study of McAnulty et al. (McAnulty et al. 1982), in cases with complete heart block only half of the patients presented with syncope – the other half had fatigue, dyspnea or chest pain. However, in a prospective study from 1970s (Dhingra et al. 1974), symptoms could be attributed to high grade AV block only in 17 % of the patients with syncope, while in a majority of cases the syncope was a result of ventricular arrhythmia or noncardiac causes. This was challenged by a more recent study from 2011 with 323 patients with bundle branch block and previous syncope (Moya et al. 2011) as bradyarrhythmia was the most common cause of syncope (63 % of the patients). Furthermore, bradyarrhythmia as the cause of syncope was detected by an implantable loop recorder in 38 % of patients with negative initial evaluation and negative electrophysiological study. The systematic diagnostic approach to syncope resulted in 220 pacemaker and 19 implantable cardioverter defibrillator implantations and with overall etiological diagnosis of syncope in 83 % of patients. Furthermore, in a

study from 2001, in patients with bundle branch block and negative electrophysiological study, most syncopal recurrences seemed to have a homogeneous mechanism that is characterized by prolonged asystolic pauses mainly attributable to sudden-onset paroxysmal AV block. In conclusion, in patients with bifascicular block and negative electrophysiological study, applying an implantable loop recorder seems reasonable, with pacemaker implantation being safely delayed until symptomatic bradycardia is documented (Brignole et al. 2001).

In the presence of a prolonged PR interval, or 1st degree AV block, the conduction delay may occur within the AV node or in the infranodal His-Purkinje system. Although individuals with a long PR interval may have a prolonged HV interval (Dhingra et al. 1981, Scheinman et al. 1982), PR interval *per se* is an unreliable indicator of a distal conduction system disease (Levites and Haft 1974, McAnulty et al. 1982) and more importantly, the presence of a prolonged PR interval associated with chronic bifascicular block does not seem to be predictive of a distal second-degree or complete heart block (Dhingra et al. 1981, McAnulty et al. 1982, Scheinman et al. 1982, Alpert and Flaker 1984). This might not apply to those with bifascicular block pattern of RBBB with concomitant LPFB (Rosenbaum et al. 1968, Rosenbaum 1970, Boule et al. 2014).

2.3 Left Bundle Branch Block

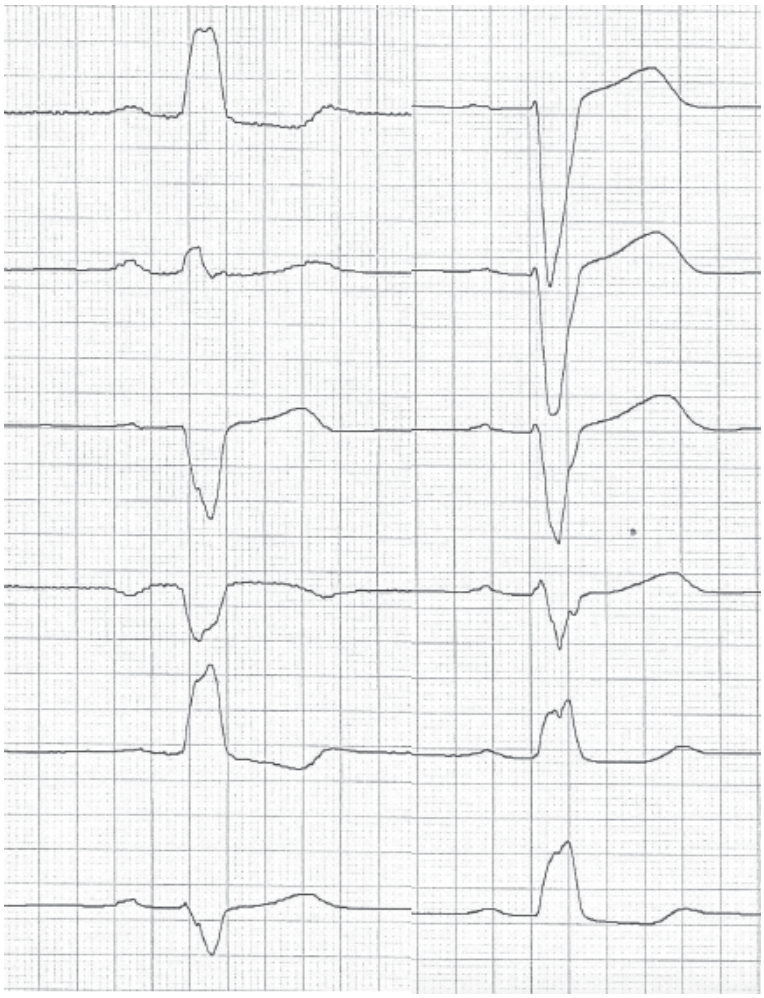
In 1909, Eppinger and Rothberger published the first experimental ECG of LBBB after cutting the left and right bundle branches in their canine experiments, though mistakenly switching the diagnosis of RBBB and LBBB. In the same year, Barker and Hirschfelder independently reported results they obtained by cutting the left main bundle of a canine heart (Barker and Hirschfelder 1909). By this time in the following year, Eppinger and Stoerck were able to find five patients with intraventricular block similar to one they experimentally produced (Eppinger 1910). In 1914, Carter published his investigation on patients with LBBB (which the author misnamed as RBBB) collected from various hospitals in London (Carter 1914). Carter found out that in some patients LBBB may be present for many years, but he also observed a frequent association with heart failure and high mortality in other patients with LBBB. Carter also depicted the original criteria for LBBB and described the frequent notching within the QRS complex and noted that the QRS duration exceeds 100 ms in bundle branch block. The literature continued switching the diagnosis of bundle branch blocks until Oppenheimer and Pardee published two autopsy cases in 1920 and proposed the diagnosis of RBBB and LBBB had been reversed (Oppenheimer and Pardee 1920). The debate was finally settled by Barker and coworkers after the electrical stimulation of the right epicardium of the human heart showed LBBB pattern, while the stimulation of the left ventricular epicardium generated RBBB pattern (Barker et al. 1930). In 1942, Wilson propounded more detailed definitions of bundle branch block after the wide availability of precordial leads, and the classic threshold for QRS duration of 120 ms for complete bundle branch block was established (Wilson 1942).

The left bundle branch system consists of left-sided His fibers, the left main stem, and the left fascicles (anterior and posterior fascicles, and septal fibers). Conduction defect may emerge in any of these structures - in most of cases with LBBB the site of the block is before the bifurcation of the left fascicles. Rosenbaum referred this type of block as a *predivisional* LBBB (Figure 3) to differentiate it from the type of block where the conduction is interrupted in both anterior and posterior divisions at the same time –a *divisional* LBBB. This divisional LBBB differs in no way from the classical predivisional ECG pattern of LBBB (Rosenbaum 1969).

After the main common bundle emerges from the central fibrous body, it gives off sheets of the conduction system forming the main left bundle branch at the base of the interleaflet triangle between the right and noncoronary leaves of the aortic valve. After running inferiorly and slight anteriorly approximately about 1 cm, the

main left bundle reaches its maximal width before it forks into left fascicles (Elizari 2017). Thus, its origin is the narrowest of point of the bundle branch, and the left bundle branch is most often damaged at its very origin where it is exposed to mechanical compression of the septal endocardium considerably thickening with advancing age, and the membranous septum underneath coming sclerotic in older age. Supporting the anatomic observations and the famous pathological studies, in a recent study from 2019 the most common site for a lesion responsible for LBBB pattern was a focal and proximal block in the left *intra*-Hisian system (Upadhyay et al. 2019).

Figure 3. Left Bundle Branch Block. Secondary ST-segment elevation can be seen in precordial leads V1 to V3 and secondary ST-depression in left lateral leads I, aVL, and V5-V6.

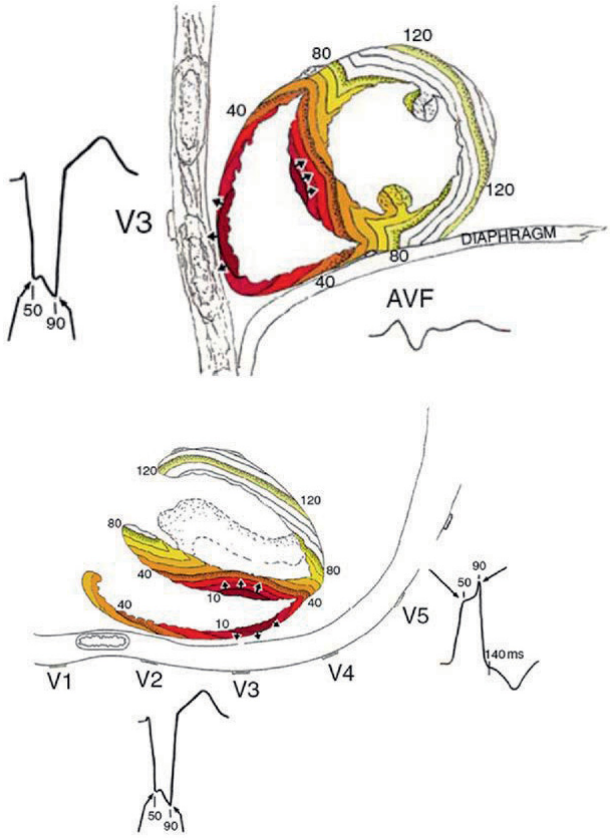


In the famous work of Lenègre in 1958 (Lenegre 1958), the author observed that the most cases of LBBB are of "mechanical" nature, substantiated by Lev (Lev 1961, Lev et al. 1963) in histopathological studies of the conduction system. The clinical disease was hypertensive or CHD or aortic disease in most cases. The lesions in the left bundle branch were located in the very origin of the branch and facing a fibrous or fibrocalcific spur-like extension of the membranous septum suggesting a mechanical rather than ischemic or inflammatory origin. The opposite was true in Rosenbaum's series as LBBB was rather of ischemic than mechanical origin (Rosenbaum et al. 1968, Rosenbaum 1970).

In the Framingham Heart Study (Schneider et al. 1979), a new-onset LBBB occurred mostly in subjects with a history of hypertension, ischemic heart disease, cardiomegaly, or a combination of these. In another study (Senesael et al. 2020), the development of new-onset LBBB was associated with elderly age and decreased left ventricular function. In the Manitoba Study of either pilots or pilots in training (Rabkin et al. 1980), LVH was associated with the development of new-onset LBBB. This association was also shown in two other studies (Peter et al. 1998, Imanishi et al. 2006). Other etiologies include previous myocardial infarction, valvular heart diseases, primary conduction diseases (Lenègre's and Lev's diseases), dilated cardiomyopathy, and other infiltrative and metabolic heart diseases and cardiomyopathies (Jain and Mehta 2003, Pérez-Riera et al. 2019), in addition to iatrogenic causes of LBBB after transcatheter aortic valve implantation as previously discussed. However, it is not unusual that LBBB is encountered without apparent CV disease in clinical practice (Jain and Mehta 2003).

In the presence of LBBB, there is a significant electrical delay between the activation of the interventricular septum and the left ventricular free wall. In normal conduction, the activation begins in both left and right ventricular endocardium. In LBBB, the activation begins only in the right ventricle and must proceeded through the interventricular septum for 40 to 50 ms to reach the left ventricular endocardium (Figure 4). It then requires another 50 ms for re-entry into the left ventricular Purkinje network and to propagate to the endocardium of the posterolateral wall. Finally, the electrical activation of the posterolateral wall requires an additional 50 ms (Grant and Dodge 1956, Selvester and Solomon 1985, Strauss and Selvester 2009, Strauss et al. 2011).

Figure 4. The Activation of Left Ventricle and QRS Morphology in Left Bundle Branch Block (LBBB). The key feature of LBBB is the presence of mid-QRS notching. The first notch represents the time when the electrical depolarization wave originating from the right ventricle reaches the left ventricular endocardium after proceeding through the interventricular septum. From the original work of Strauss et al. (Strauss et al. 2011)



In LBBB, the ST-segment and T wave are generally directed opposite of the mean QRS complex. Abnormalities in the ST-segment and T wave occur as a direct result of changes in the sequence and duration of the ventricular depolarization and are referred as secondary repolarization changes (Figure 3). While the recognition of these secondary repolarization abnormalities is simple, they may obscure the diagnosis of myocardial infarction. Occasionally, LBBB is accompanied with left axis deviation. In the presence of left axis deviation the ventricular activation happens latest in the anterior wall of the left ventricle (Sciarra et al. 2018).

When LBBB is associated with a previous infarction of the lateral free wall, left lateral leads may show RS complex with a broad S wave (>40 ms). The presence of triphasic qRS complex in V5-V6 suggest a massive previous anterolateral and septal infarction, referred as "dome and dart" QRS complex in the older literature (Schamroth 1975). Furthermore, the R wave may loss its amplitude in lead V6 and a "W-shaped" QR complex may be observed in precordial leads V1 to V4-V5 in a massive anteroseptal infarction. A notch of 40 ms in duration in the ascending ramp of the S wave has been referred as Cabrera's sign (Cabrera and Friedland 1953) and has decent specificity but poor sensitivity in the diagnosis of previous infarction (Kindwall et al. 1986). Notch in the ascending ramp of the R wave in left lateral leads has been referred as Chapman's sign (Chapman and Pearce 1957) but has a poor specificity in the diagnosis of previous myocardial infarction and provides no useful clinical information (Kindwall et al. 1986). Increase of voltage of the initial R wave in V1 and appearance of Q waves in leads V5 and V6 is diagnostic of a large antero-apical infarction of the interventricular septum. Thus, the presence of Q waves in these leads should not exclude patients from a diagnosis of LBBB as they do in the traditional definitions of LBBB (Table 1). However, a small initial Q wave may be seen in lead aVL in absence of any myocardial pathology if the left septal fascicle emerges before the block area and the middle-septal activation is preserved (Perez-Riera et al. 2019).

2.3.1 Defining Left Bundle Branch Block

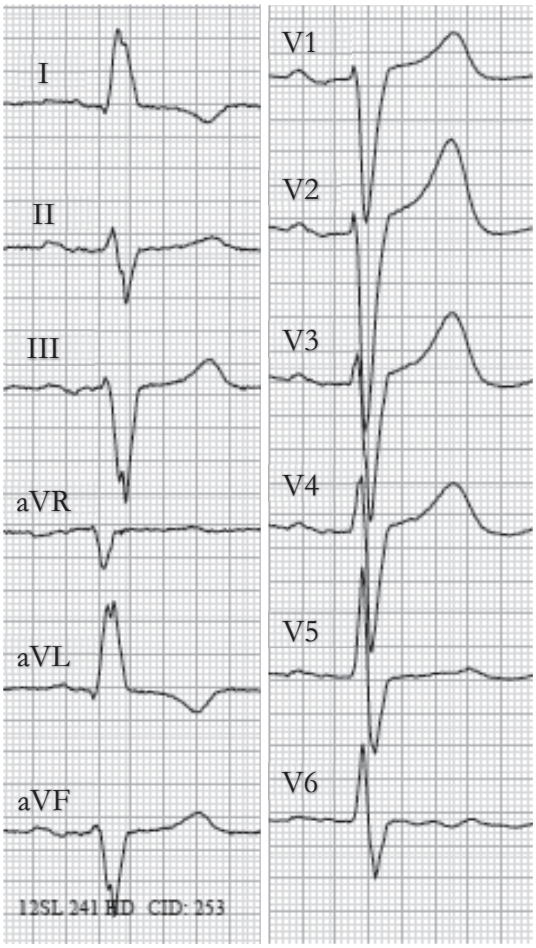
For the diagnosis of complete LBBB, the cut-off value for the QRS duration has traditionally been ≥120 ms. The different criteria for the definition of LBBB are summarized in Table 1. Both the guidelines of the American College of Cardiology and the American Heart Association (Surawicz et al. 2009, Kusumoto et al. 2018), and the European Society of Cardiology require a broad notched or slurred R waves in left lateral leads in absence of Q waves in leads V5 and V6, and a QRS duration ≥120 ms. Occasionally, RS pattern in V5 and V6 can be seen, attributed to displaced transition of QRS complex.

Table 1. Definitions of Left Bundle Branch Block
ACC = American College of Cardiology; AHA = American Heart Association; HRS = Heart Rhythm Society; ESC = European Society of Cardiology

	Conventional (Minnesota)	ACC/AHA/HRS (2009/2018)	ESC (2013)	Strauss (2011)
QRS duration	≥120 ms	≥120 ms	≥120 ms	Men ≥140 ms, Women ≥130 ms
QS or rS wave	-	-	V1	V1, V2
No Q wave	I, II, aVL, V5-V6	I, V5-V6	V5-V6	-
R-peak time (≥60 ms)	I, II, aVL, V5-V6	V5-V6	-	-
R wave notching or slurring	-	I, aVL, V5-V6	"Frequently" in leads I, aVL, V5-V6	≥ 2 leads: I, aVL, V1, V2, V5, V6
Discordant ST-segment and T wave	-	"Usually"	-	-

Authors have argued for stricter criteria for the diagnosis of LBBB (Figures 4 ja 5). In 1956, Grant and Dodge studied 128 patients with a QRS duration ≥120 ms (Grant and Dodge 1956). They observed that in case of a complete LBBB, the initial electrical QRS forces must change in direction due to altered activation of the interventricular septum, and the QRS duration prolongs significantly more than 40 ms with the development of LBBB (Figure 4). Based on these two observations, they proposed that ⅓ of ECGs classified as LBBB were incorrectly diagnosed. In 1984, Vassallo performed endocardial catheter mapping in 18 patients with LBBB by conventional ECG criteria, and found that ⅓ of ECGs classified as LBBB were misdiagnosed (Vassallo et al. 1984), just as Grant and Dodge had observed 28 years earlier. In 2004, Auricchio studied activation sequences of 24 patients with LBBB by conventional criteria using 3-dimensional contact and noncontact endocardial mapping, and found out that ⅓ of patients did not have the required minimum 40 ms delay between right and left endocardial activations (Auricchio et al. 2004). Based on these three key studies, Strauss et al. proposed new criteria for "strict" LBBB: QRS duration ≥140 ms (men) or 130 ms (women), QS or rS in leads V1 and V2, and mid-QRS notching or slurring (Figure 4) in ≥2 of leads I, aVL, V1, V2, V5, and V6 (Strauss et al. 2011).

Figure 5. ECG from a 60-year-old male (QRS duration 120 ms). Distinct notching of the R wave is present in leads I and aVL, misleadingly resembling left bundle branch block (LBBB), but the typical LBBB morphology is not present in precordial leads. The ECG actually represents a non-specific intraventricular conduction delay as a result of left ventricular hypertrophy with left anterior fascicular block. Notching is probably explained by regional myocardial scarring and fibrosis – indeed, the patient's history revealed chronic coronary heart disease with three previous percutaneous coronary interventions.



In a pioneer work of Upadhyay in 2019, 36 % of patients with LBBB by conventional criteria showed intact Purkinje activation, representing an intraventricular conduction defect with diffuse distal conduction or intramyocardial disease (Upadhyay et al. 2019). When LBBB was defined by the Strauss criteria, the proportion of patients with intact Purkinje activation dropped to 19 % in this study.

2.3.2 Prevalence of Left Bundle Branch Block

In epidemiologic studies conducted during the last 50 years, the overall prevalence of LBBB in the population has been reported around 0.1 – 1 % (Fahy et al. 1996, De Bacquer et al. 2000, Haataja et al. 2013). The prevalence of LBBB is known to increase with age (Fahy et al. 1996), rising up to 5 – 6 % in elderly individuals over 80-years of age (Eriksson et al. 1998). Estimates of CHD in individuals with LBBB have varied from 27 to 45 % (Schneider et al. 1979, Thrainsdottir et al. 1993, Eriksson et al. 1998, Zhang et al. 2012, Badheka et al. 2013) in epidemiologic studies. Approximately one third of the patients with LBBB have shown eventually to develop heart failure in the literature (Schneider et al. 1979, Eriksson et al. 2005).

Among the pilots of the United States Air Force in their forties (Rotman and Triebwasser 1975), the prevalence of CHD was only 9 % in those with LBBB, but this was significantly higher than in those with RBBB even when adjusted for age. In addition, hypertension was significantly more common in the clinical evaluation in those with LBBB than in those with RBBB. In another study of 298 asymptomatic airmen undergoing cardiac catheterization in their forties (Froelicher et al. 1977), significant CHD (50 % or more luminal occlusion) was found in 24 % of subjects with LBBB (overall n = 34) and 20 % of subjects with RBBB (overall n = 41), comparable to those airmen without bundle branch block in 1970s.

In the general heart failure population, LBBB is present in 15 – 25 % of the subjects (Baldasseroni et al. 2002, Khan et al. 2007, Tabrizi et al. 2007, Abdel-Qadir et al. 2011, Barsheshet et al. 2011, Cinca et al. 2013, Lund et al. 2013). The prevalence of LBBB is lower in patients with heart failure with preserved ejection fraction (Baldasseroni et al. 2002, Barsheshet et al. 2008, Lund et al. 2013), and higher patients with heart failure with reduced ejection fraction (Wang et al. 2008) with prevalence increasing among patients with more severely impaired left ventricular function (Baldasseroni et al. 2002, Barsheshet et al. 2008, Abdel-Qadir et al. 2011, Lund et al. 2013). In the Italian Congestive Heart Failure Outpatient Registry (Baldasseroni et al. 2002) of unselected patients with chronic heart failure of different causes, dilated cardiomyopathy was the etiology of heart failure in 49 % and ischemic heart disease was prevalent in 43 % of the patients with LBBB. Similar rates of dilated cardiomyopathy and ischemic heart disease were also reported on a Spanish study (Cinca et al. 2013). A Canadian study (Abdel-Qadir et al. 2011) reported a higher rate of ischemic heart disease (60 %) as the etiology of heart failure in patients with LBBB. The prevalence of CHD was even higher (81 %) in subjects with LBBB in an Israeli study (Barsheshet et al. 2008). The rate of prior myocardial infarction has been

reported around 40 – 50 % in subjects with LBBB and heart failure in these studies (Tabrizi et al. 2007, Barsheshet et al. 2008, Abdel-Qadir et al. 2011).

2.3.3 Mechanism of Harm in Left Bundle Branch Block

The deleterious effect of LBBB on left ventricular systolic and diastolic function has been established even in subjects without overt heart disease (Grines et al. 1989, Özdemir et al. 2001). In patients with isolated LBBB who appear otherwise healthy, left ventricular ejection fraction appears normal or only mildly reduced (Grines et al. 1989, Aalen et al. 2019). In heart failure and LBBB, left ventricular function is usually markedly reduced and those with a preserved left ventricular function present a minority of patients (Baldasseroni et al. 2002, Tabrizi et al. 2007, Barsheshet et al. 2008, Abdel-Qadir et al. 2011). Interestingly, a functional decline measured by change of left ventricular ejection was found in over one third of the patients in a retrospective study of patients with LBBB and preserved ejection fraction (Sze et al. 2017). Recently, it was demonstrated that subjects with LBBB are hypersensitive to elevated afterload as moderate elevation of systolic arterial pressure led to marked reductions of left ventricular function, measured by decrease of ejection fraction and global longitudinal strain in echocardiography (Aalen et al. 2019).

One of the most likely causes of left ventricular functional decline in LBBB is the associated mechanical dyssynchrony (Vaillant et al. 2013). This is supported by the fact that biventricular pacing, which corrects dyssynchrony, is associated with a reverse in the left ventricular mechanical decline as well as with better outcomes in patients with symptomatic heart failure and LBBB (Linde et al. 2013, Vaillant et al. 2013, Goldenberg et al. 2014). In LBBB, the early activated septum contracts when the left lateral wall is relaxed. This leads to a significant loss of the septal contribution to left ventricular function and is a major stimulus for left ventricular remodeling in patients with heart failure (Smiseth and Aalen 2019). In an animal model (Vernooy et al. 2004), LBBB induced unfavorable ventricular dilation, remodeling and asymmetric hypertrophy even in normal hearts.

Dyssynchrony in LBBB affects both systolic and diastolic function of the heart. LBBB prolongs isovolumetric relaxation and thereby reduces left ventricular diastolic filling time (Özdemir et al. 2001, Smiseth and Aalen 2019). In addition, LBBB induces and aggravates mitral regurgitation by several mechanisms, which prevent normal coaptation of the valve leaflets (Smiseth and Aalen 2019). Finally,

the presence of LBBB has been associated with a predisposition to malignant tachyarrhythmias (Zimetbaum et al. 2004, Aro et al. 2011).

2.3.4 Prognostic Implications

In 1930s, mortality from LBBB was 60 % within the first year (Perera et al. 1942). Meanwhile, in individuals who were evaluated for life insurance in the United States in 1930s and 1940s (n = 193) (Rodstein et al. 1951), the prognosis of LBBB (n = 52) was associated with only a little demonstrable CV impairment in absence of overt CV disease. Likewise, among predominantly healthy pilots of the United States Air Force in their forties (Rotman and Triebwasser 1975), LBBB (n = 125) did not increase CV death or CV morbidity compared to subjects with RBBB in over 10 years of follow up in 1960s.

In the Manitoba Study, pilots or pilots in training (men; mean age 31 years) with no clinical evidence of ischemic heart disease were followed for average 29 years (n = 3 983) (Rabkin et al. 1980). The five-year incidence of sudden death as the first manifestation of heart disease was 10 times greater in men with LBBB than in those without it. More specifically, the CV mortality was 21 %, and 83 % of these suffered sudden cardiac death. LBBB developed during the observation period in all but one case, in whom it was present at entry.

The Framingham Heart Study was the first large study in CV disease epidemiology. Since 1949, a representative sample of the adult population of Framingham (n = 5 029), Massachusetts, has been followed for the development of CV diseases. During 18 years of observation 55 people developed LBBB at the mean age of 62 years. Throughout the entire period of observation only 11 % remained free of clinically apparent CV diseases, and 50 % died of CV diseases within 10 years of the onset of LBBB. After adjustments for CV morbidity, LBBB was independently associated with increased mortality in men but not in women (Schneider et al. 1979). In another study of the Framingham Heart Study population (n = 1 759) (Dhingra et al. 2006), participants with LBBB (n = 26) were more likely to develop heart failure than those with QRS duration <100 ms.

In a report from the National Health and Nutrition Examination Survey (n = 8 527) (Badheka et al. 2013), LBBB (n = 55) was associated with increased CV mortality. Remarkably, only three patients had no prevalent CV disease (excluding hypercholesterolemia and hypertension). In the Atherosclerosis Risk in Communities study (n = 15 408) (Zhang et al. 2016) during a mean 21 years of

follow-up, LBBB (n = 90) was associated with increased all-cause and CHD mortality. In another study of the same cohort (n = 14 478) (Zhang et al. 2015), LBBB (n = 75) was associated with increased risk of novel heart failure. In a large screening study of Irish Heart Foundation (Fahy et al. 1996), subjects with LBBB (n = 112) without apparent heart disease (self-reported) or hypertension had similar overall mortality, but increased rate of CV mortality, as compared to age- and sex-matched controls without bundle branch block. CV disease also developed in more patients with isolated LBBB than in controls during a mean follow-up of 9.5 years.

In a study of men born between 1915 and 1925 in Sweden (n = 7 392) (Eriksson et al. 2005), in middle-aged men with no history of myocardial infarction or stroke LBBB (n = 46) was associated with acute myocardial infarction, overall and CV mortality, heart failure, and the risk of a high-degree AV block and pacemaker implantation. The rate of AV block was 15 % over a period of 28 years. Excluding patients with possible anginal symptoms and dyspnoea on exertion did not have impact on results.

In the Women's Health Initiative study (n = 66 450) (Zhang et al. 2012), LBBB (overall n = 714; without CV disease n = 408) was associated with CV mortality but not with overall mortality in women without CV disease at baseline (n = 52 663). In those with a prevalent CV disease, LBBB was associated with both overall and CV mortality. In another study of the same cohort (Zhang et al. 2013) LBBB (n = 680) was a predictor of incident heart failure in women, and the risk was even more pronounced in women with a longer QRS duration (≥140 ms).

In a retrospective cohort study of Olmsted County with asymptomatic patients and normal left ventricular ejection fraction and no heart disease (Miller et al. 2005), those with LBBB (n = 420) had higher mortality compared to the age and gender matched control group even after adjusting for risk factors, and had earlier occurrence of CV events than those with RBBB (n = 303) during overall follow-up of 20 years. However, no statistical difference in mortality was shown among patients with risk factor–free LBBB (n = 66), RBBB (n = 97), and controls (n = 487).

The Reykjavik Health Survey (n = 17 489) (Hardarson et al. 1987) established an association between LBBB (n = 44) and cardiomyopathy, and reported increased mortality from cardiomyopathy but no increased risk of overall mortality in patients with LBBB. The 40-year follow-up study of atomic bomb survivors in Hiroshima and Nagasaki (n = 17 361) (Imanishi et al. 2006) also reported no increased all-cause mortality, but mortality from heart failure was more common in subjects with incident LBBB (n = 110).

In a study of adults referred for nuclear exercise testing to evaluate a known (over 50 % of patients) or suspected coronary artery disease without heart failure (n = 7 073) (Hesse et al. 2001), patients with LBBB (n = 150) had increased risk of death. In patients aged ≥55 years with a stable CV disease (CHD or prior myocardial infarction was present in over 80 % and 50 % of the patients, respectively) or diabetes with ≥1 CV risk factor(s) but without heart failure (n = 9 541) (Sumner et al. 2009), both prevalent (n = 246) and incident (n = 148) LBBB were associated with increased CV and overall mortality, sudden cardiac death and new-onset heart failure. In a large study of patients with stable CHD (n = 15 609) (Freedman et al. 1987), LBBB (n = 250) was an independent predictor of mortality, and patients with LBBB had more often a multivessel disease.

In LBBB patients, left axis deviation ≤−30° is known to be associated with more severe conduction system disease and structural pathology of the left ventricle, implying more severe prognosis (Dhingra et al. 1978). In the work of Dhingra, absence of organic heart disease was only seen in cases of LBBB with normal axis. Left axis deviation could have significant implications for biventricular pacing. In this case, placing the left ventricular lead in the anterolateral position might allow for dyssynchrony correction (Tan et al. 2020).

2.3.4.1 Prognosis in Myocardial Infarction

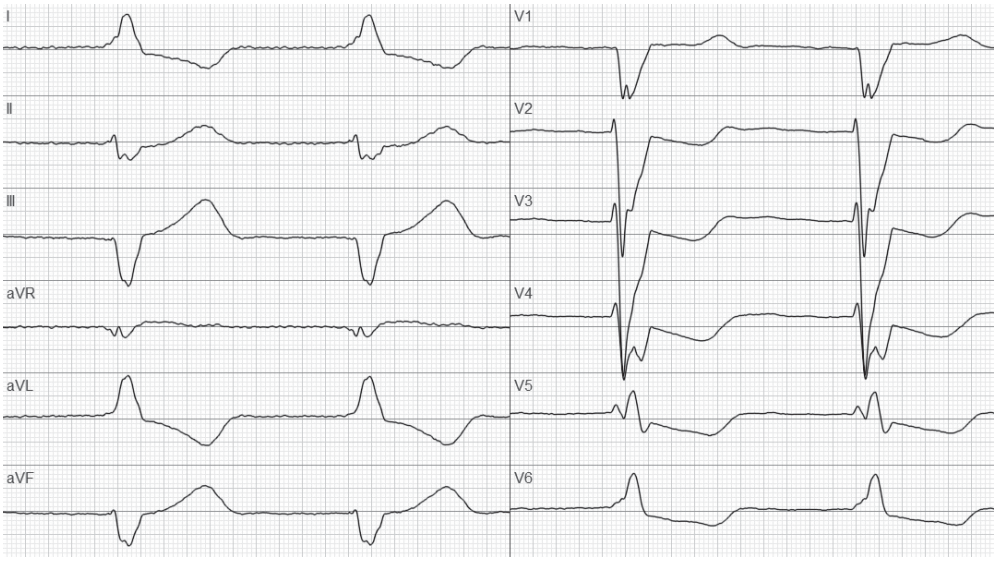
In a setting of acute myocardial infarction, the prevalence of LBBB has been reported as 5 – 7 % (Go et al. 1998, Nikus et al. 2012, Widimsky et al. 2012, RIKS-HIA Annual Report 2013) with a rate of new-onset LBBB around 2 – 4 % (Al-Faleh et al. 2006, Wong et al. 2006, Widimsky et al. 2012, Yeo et al. 2012, Pera et al. 2018), and therefore represents an important clinical subset of patients. The proximal left bundle branch, before the bifurcation of the fascicles, has a dual blood supply and is perfused by both AV nodal artery of the right coronary artery and branches of the left anterior descending artery. Accordingly, severe two- or three-vessel disease should typically be present for a new LBBB to develop in a setting of acute myocardial infarction (Frink and James 1973, Nikus et al. 2020).

Historically, in the prethrombolytic era, the prevalence of new LBBB in the setting of acute myocardial infarction was 5% to 11% and was associated with 40 to 50 % in-hospital mortality (Norris and Croxson 1970, Gould et al. 1972, Hindman et al. 1978, Stephenson et al. 2007). Studies in the fibrinolytic era denoted a downward trend in both incidence and short-term mortality (18 – 40 %) associated with new LBBB (Fibrinolytic Therapy Trialists 1994, Sgarbossa et al. 1996,

Stephenson et al. 2007), though the mortality remained high. In the modern era of primary percutaneous coronary intervention, the presence of new-onset LBBB has been associated with a higher incidence of cardiogenic shock at presentation (Stenestrand et al. 2004) and higher rates of in-hospital (10 – 15 %), 1-month (15 – 20 %), and 1-year (25 %) mortality in a setting of acute myocardial infarction (Stenestrand et al. 2004, Widimsky et al. 2012, Brown et al. 2013, Pera et al. 2018). Large comorbidity and myocardial dysfunction are the main explanations for the higher mortality (Stenestrand et al. 2004).

Diagnosis of acute myocardial infarction in the presence of LBBB has been experienced challenging in the clinical setting (Figure 6). In real life setting, reperfusion therapy is delayed in patients with LBBB even for those who ultimately receive a biomarker diagnosis of acute myocardial infarction (Krumholz et al. 1997, McNamara et al. 2006, Stephenson et al. 2007, Tricomi et al. 2008, Archbold et al. 2010). In 1996, Sgarbossa proposed ECG criteria and score for diagnosis of acute myocardial infarction in the presence of LBBB (Sgarbossa et al. 1996). These *Sgarbossa rules* consist of three rules: 1) concordant ST-segment elevation ≥1 mm in any lead (score 5); 2) concordant ST-segment depression ≥1 mm in any of the leads V1 to V3 (score 3); and 3) discordant ≥5 mm ST-segment elevation (score 2). Sgarbossa proposed requiring at least 3 points from the following criteria for diagnosis of acute myocardial infarction in the presence of LBBB (Figure 6). In a systematic review (Tabas et al. 2008), although the Sgarbossa score ≥3 was highly specific (98 %) for occlusion, the sensitivity was only 20 %. In 2012, Smith proposed the rule of proportional ST-segment elevation or ST-segment depression for diagnosis of acute coronary occlusion myocardial infarction in the presence of LBBB (Smith et al. 2012). In addition to the original first two Sgarbossa rules, the third rule is replaced with "excessively discordant ST elevation in any lead with ST-segment elevation ≥25 % of the preceding S wave amplitude". The sensitivity and specificity of this Smith modified Sgarbossa rule were 91 % and 90%, respectively, though the ST-segment elevation ≥20 % of the preceding S wave amplitude was still quite specific and even more sensitive for acute occlusion of epicardial coronary artery. Smith also proposed another rule: any single lead with proportionally excessively discordant ST-segment elevation or ST-segment depression ≥30 % of the previous S or R wave (Figure 6). The sensitivity and specificity of the rule were 64 % and 98 % in the validation study (Meyers et al. 2015).

Figure 6. A 57-year male with a history of atrial fibrillation, hypertension and LBBB in his prior ECG presented to the emergency department with two hours of chest pain radiating to his neck and left arm. The ST-segment elevation myocardial infarction equivalent instance was not recognized, and the cardiac catheterization team was not activated ahead. Precordial leads V2 to V4 show concordant ≥1 mm ST-segment depression, positive for Sgarbossa criteria. In addition, there is excessively discordant ST-segment depression in lead V5 (ST/R = 40 %). Emergency percutaneous coronary intervention was performed with a door-to-balloon time of 35 minutes, and a large thrombus was found occluding the right coronary artery.



2.3.4.2 Prognosis in Heart Failure

In a large study from the Swedish Heart Failure Registry (n = 25 171) (Lund et al. 2013), LBBB (n = 4 028) was associated with worse prognosis regardless of the left ventricular systolic function. Similar observation was made in a Canadian cohort of patients hospitalized for acute heart failure (n = 9 082) (Abdel-Qadir et al. 2011) as patients with LBBB (n = 1 480) had a 10 % increased risk of mortality compared to those without bundle branch block after adjustment for heart failure classification. LBBB was also associated with both future heart failure and CV hospitalizations at 5-year follow up in this study. In a report from Italian Congestive Heart Failure Outpatient Registry (n = 5 517) (Baldasseroni et al. 2002), LBBB (n = 1 391) was independently associated with increased mortality and sudden cardiac death regardless of left ventricular ejection fraction. In a Spanish study of patients with chronic heart failure (n = 2 254) (Cinca et al. 2013), after multiple adjustments for

therapy and left ventricular function and mass, LBBB (n = 532) was associated with cardiac and pump failure death.

The Swedish Register of Cardiac Intensive Care study of patients with symptomatic heart failure admitted to a coronary care unit (n = 21 685) (Tabrizi et al. 2007) established a very high mortality in patients with LBBB (n = 4 395) – mortality rates at 1, 5, and 10 years were 32 %, 69% and 90 %, respectively. In the whole study group, LBBB was associated with increased 3-, and 5-year mortality. In a subgroup of patients with available echocardiographic measurements for left ventricular ejection fraction (n = 3 327), LBBB (n = 679) was not associated with increased mortality *per se*. However, as patients with available echocardiographic measurements had significantly better long-term survival, the results from this subgroup might not apply to the rest of the study population.

In another study of patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction (n = 2 962) (Wang et al. 2008), LBBB (n = 909) was associated with increased mortality and hospitalization for heart failure as compared to patients with QRS duration <120 ms. When the analysis was repeated comparing the survival among patients with QRS duration ≥120 ms, LBBB was not associated with increased mortality. Conversely, in a smaller study from Heart Failure Survey in Israel database (n = 1 888) (Barsheshet et al. 2011), LBBB (n = 306) was not associated with increased mortality in patients with reduced left ventricular function.

In the post hoc analysis from the treatment of preserved heart failure with an aldosterone antagonist trial (n = 3 426) (Joseph et al. 2016), LBBB (n = 134) was associated with increased heart failure hospitalizations even after adjustment for age and sex, but not with excess mortality. In the earlier report from Heart Failure Survey in Israel database (n = 698) (Barsheshet et al. 2008), no increased mortality was seen in hospitalized patients with preserved left ventricular function and LBBB (n = 45).

In patients with a history of CHD with depressed left ventricular function and a documented nonsustained ventricular tachycardia (n = 1 638) (Zimetbaum et al. 2004), LBBB (n = 131) was associated with increase of arrhythmic death and total mortality.

2.3.5 Cardiac Resynchronization Therapy

The Framingham Heart Study researchers related the natural history of congestive heart failure to very grave prognosis in 1970s – more than half of the subjects were dead within five years after the incidence of heart failure (McKee et al. 1971). Despite

remarkable improvements in medical therapy (Captopril Multicenter Research Group 1983, Swedberg and Kjekshus 1987, Yusuf et al. 1992) the five-year mortality rates remained over 60 % in the beginning of the 21st century (Owan et al. 2006). In the early 2000s, the first randomized trials demonstrated the benefits of cardiac resynchronization therapy (CRT) on symptoms, exercise capacity and left ventricular structure and function (Cazeau et al. 2001, Abraham et al. 2002, Auricchio et al. 2002), but were underpowered to evaluate the effect on mortality (Rivero-Ayerza et al. 2006). Meta-analyses of the major randomized trials concluded that CRT reduces mortality and heart failure hospitalizations compared to optimal medical therapy in patients with advanced heart failure with reduced ejection fraction (Rivero-Ayerza et al. 2006), and even in patients with mild, New York Heart Association functional class I and II heart failure (Al-Majed et al. 2011, Selcuk et al. 2011).

However, CRT was effective in reducing adverse clinical events in patients with heart failure and a baseline QRS interval of 150 ms or greater, but CRT did not reduce events in patients with a QRS duration less than 150 ms (Sipahi et al. 2011), as shown in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (Moss et al. 2009). Additional analysis of this study also considered thresholds of QRS duration separately for men and women. The benefit from CRT to reduce heart failure events was highly significant in women beginning at QRS duration ≥130 ms and there was no benefit in men with QRS duration <140 ms (Zareba et al. 2011), as also shown in a meta-analysis of five other major CRT trials (Linde et al. 2018). Subsequent analysis of this trial also showed that patients with LBBB derive substantial clinical benefit from the device while patients without LBBB (RBBB or non-specific IVCD) had a non–statistically significant increase in adverse events (Zareba et al. 2011). Although response to CRT goes beyond the restoration of electrical synchrony and cannot be used as proof of concept, the analyses agreed with the proposed criteria of Strauss et al. (Strauss et al. 2011) that the minimum QRS duration threshold for defining complete LBBB in women is 130 ms and in men 140 ms along with mid-QRS notching or slurring. In a retrospective cohort study comparing four definitions of LBBB in patients who underwent CRT device implantation (Jastrzebski et al. 2018), LBBB was the major determinant of all-cause mortality with the Strauss definition having the lowest hazard ratio of the four studied definitions, carefully suggesting that the Strauss definition of LBBB could identify better patients with "true" LBBB who therefore benefit more from CRT. In another retrospective study, the definition of LBBB was indeed shown to have significant impact on outcome in CRT patients (Caputo et al. 2018).

2.4 Right Bundle Branch Block

Anatomically, the right bundle branch is a direct continuation of the main common bundle. After giving off the left sided fibers at the pseudobifurcation, the branching portion of the bundle of His continues directly as the right bundle branch. The right bundle branch, unlike the left bundle, does not divide until it reaches the anterior papillary muscle (Uhley 1979). The proximal right bundle receives its blood supply mainly from the septal branch of the left anterior descending artery, and in approximately half of the cases jointly with the AV nodal artery of the right coronary artery (Frink and James 1973). The distal part of the right bundle is mainly supplied by the branches of the left anterior descending.

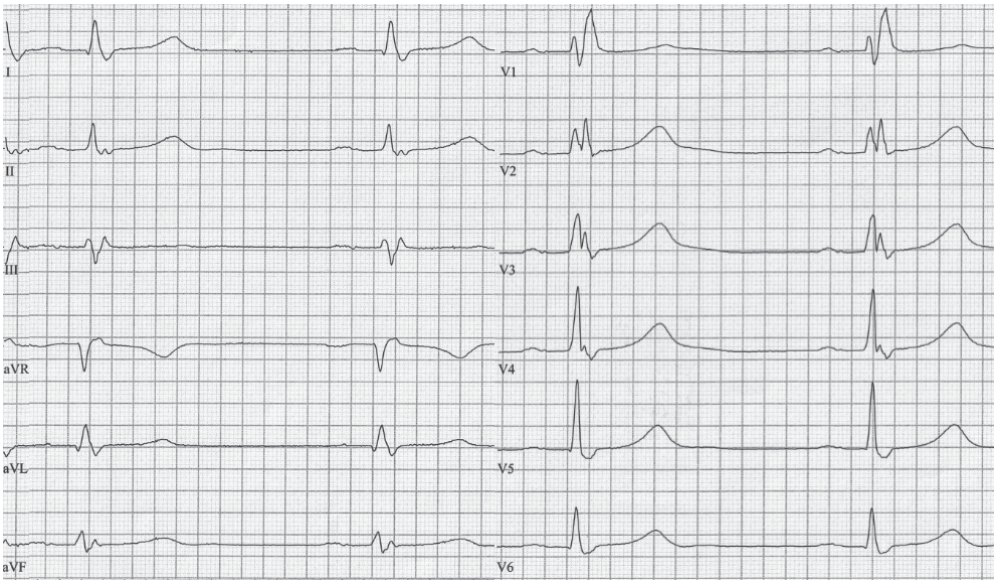
In the presence of a complete block in the right bundle branch, the initial ventricular activation begins in the middle-third of the left septal surface as in normal conduction. The left ventricular endocardium is activated normally via the rapidly conducting Purkinje system (Strauss and Selvester 2009), producing the descending ramp of the initial r wave in lead V1 and the ascending R wave in left lateral leads. Concomitantly with the final left ventricular activation in the high lateral wall, the stimulus goes through the interventricular septum from left to right, where it suffers a noticeable dromotropic delay, activating the left part of the right septum and producing the nadir of the S wave in precordial lead V1. From the septal breakthrough site, activation slowly spreads towards the anterior region and to the rest of the right ventricle so that the latest activated regions are the right lateral wall and the right outflow tract (Fantoni et al. 2005), producing the characteristic wide R' wave in the right precordial lead V1 and the wide S wave in left lateral leads (Figure 7).

In 1958, Lenègre studied 25 cases of RBBB post-mortem. In his histopathologic studies the etiology of the lesion in the right bundle branch was usually sclerodegenerative and most often located in the middle portion, and a complete RBBB was most often found in hypertensive, CHD and aortic disease with fewer cases in congenital, mitral and pulmonary lesions. (Lenegre 1958, Lev 1960).

The prevalence of RBBB in the general population is 0.2 – 2.3 % with the prevalence increasing with age (Thrainsdottir et al. 1993, Fahy et al. 1996, Zhang et al. 2012, 2016, Badheka et al. 2013), rising up to 14 % in elderly individuals over 80-years of age (Eriksson et al. 1998). Significant difference in prevalence between men and women have been reported, and males have a higher prevalence of RBBB than women (Thrainsdottir et al. 1993, Badheka et al. 2013, Haataja et al. 2013). Estimates of CHD in individuals with RBBB have varied from 25 to 46 % (Schneider et al.

1979, Thrainsdottir et al. 1993, Eriksson et al. 1998, Zhang et al. 2012, Badheka et al. 2013).

Figure 7. Right Bundle Branch Block.



Among predominantly healthy pilots of the United States Air Force in their forties (Rotman and Triebwasser 1975), the prevalence of clinically diagnosed CHD (with typical angina or previous myocardial infarction) was only 2 % in those with RBBB. A selective coronary angiography (done only to 15 % of those with RBBB) revealed a significant coronary obstruction (>50 % luminal occlusion) in 6 % of these. In another study of 298 asymptomatic airmen undergoing cardiac catheterization in their forties (Froelicher et al. 1977), significant CHD was found in 20 % of subjects with RBBB (overall n = 41), comparable to those airmen without bundle branch block in 1970s.

In the general heart failure population, the prevalence of RBBB has been reported 5 – 10 % (Baldasseroni et al. 2003, McCullough et al. 2005, Khan et al. 2007, Barsheshet et al. 2008, Wang et al. 2008, Abdel-Qadir et al. 2011, Cinca et al. 2013). Dilated cardiomyopathy as the etiology of heart failure is significantly lower in RBBB than in patients with LBBB, as shown in a Spanish study with the prevalence of dilated cardiomyopathy 16 % and 39 % in patients with RBBB and LBBB, respectively (Cinca et al. 2013). In a report from the Italian congestive heart failure database (Baldasseroni et al. 2003), half of the subjects with LBBB and one fifth of

the subjects with RBBB had dilated cardiomyopathy. Conversely, ischemic heart disease is more often the etiology of heart failure in RBBB than in LBBB with a prevalence of 60 % in RBBB (Baldasseroni et al. 2003, Abdel-Qadir et al. 2011).

The distal part of the branching portion of the bundle of His, the pseudobifurcation, is the most vulnerable part of the branching segment. As the right bundle branch and the anterior division of the left bundle have a common origin, they can well be injured together (Elizari 2017). Calcification of the aortic ring or any part of the left side of the cardiac skeleton extending to the bundle may provoke RBBB with concomitant LAFB. The overall prevalence of RBBB with LAFB was reported as approximately 1 % in the original work of Rosenbaum et al. (Rosenbaum et al. 1968), a rate higher than it has been reported in the Western general population probably due to a high incidence of Chagas cardiomyopathy. In countries where Chagas disease is not endemic, CHD and hypertension account for most cases of RBBB with LAFB, followed by Lenègre's and Lev's diseases and aortic valve disease (Elizari et al. 2013). The prevalence of RBBB with LAFB has been only 0.1 – 0.4 % and approximately 10 % to 30 % of all RBBBs in the Western general population studies (Schneider et al. 1980, Zhang et al. 2012, 2016), with prevalence increasing in those with concomitant CHD. Approximately 40 – 50 % of the subjects with RBBB and LAFB have concomitant CHD (Schneider et al. 1980, Zhang et al. 2013).

Differential diagnosis of RBBB with LAFB comprise RBBB with left axis deviation as a result of emphysema, straight back syndrome & other chest deformities and congenital heart disease. Albeit the clinical picture should be taken into account, LAFB is unlikely when S wave is deeper in lead II than lead III and a forementioned etiology ought to be considered in these cases (Elizari et al. 2013).

Masquerading bundle branch block should be considered when there is RBBB pattern in the precordial leads but LBBB pattern in the limb leads. The term coined since the entry of Richman in 1954 though it was erroneously called "LBBB masquerading as RBBB" (Richman and Wolff 1954). Masquerading bundle branch block is not a specific entity but a result of RBBB with advanced LAFB, severe LVH or a focal block in the anterolateral wall of the left ventricle as a result of myocardial infarction or fibrosis (Rosenbaum et al. 1973). Since the pioneer studies of Rosenbaum and colleagues (Rosenbaum et al. 1968, 1973, Rosenbaum 1970), we know two types of masquerading bundle branch block exist: the standard masquerading block, and the precordial masquerading block. In the latter, the pattern of RBBB is observed in the right precordial leads but LBBB pattern in left precordial leads. These two types may be seen to co-exist in ¼ of the cases, and RBBB can be recognized by the typical pattern in V1. However, LAFB may eventually conceal the typical RBBB pattern

even in the right precordial leads in such a way the ECG diagnosis can be mistaken and RBBB totally missed (Rosenbaum et al. 1973, Elizari et al. 2013). Masquerading bundle branch block is a very rare and is seen in a subgroup of advanced age and heart disease (Bayés de Luna et al. 1988). Its prevalence is unknown. The block was not as rare in Rosenbaum's series (Rosenbaum et al. 1968) in which there was a high incidence of Chagas cardiomyopathy.

2.4.1 Prognostic Implications

In 1925, Oppenheimer and Rothschild on the basis of observations on patients with RBBB pointed out that patients with this type of conduction delay might have a better prognosis than those with a lesion in the left bundle branch (Oppenheimer et al. 1925). In 1930s, the mortality was 50 % within three years in patients with RBBB (Perera et al. 1942). Likewise, in a review of hospitalized patients with RBBB (n = 281) from 1940s the mean survival was 3.9 years (Messer et al. 1951). In the Finnish cohort of ≥ 65-year-old subjects (n = 697) of the Seven Countries study (Tervahauta et al. 1996) in 1980s, 5-year rates of fatal myocardial infarction and mortality were 21 % and 52 % for RBBB (n = 33), respectively.

However, in 1950s, Reush and Vivas found out that RBBB was associated with heart disease in 62 % of cases – only three of 38 subjects without heart disease died during seven years of evaluation (Reusch and Vivas 1959). In a study of individuals who were evaluated for life insurance in the United States in 1930s and 1940s (n = 193), the prognosis related to RBBB (n = 131) was considered good and not to imply excessively high mortality in absence of other major cardiac abnormalities (Rodstein et al. 1951). Rotman et al. also described that the prognosis in predominantly healthy aircrew members with RBBB is good, especially in absence of CV disease (Rotman and Triebwasser 1975).

In the Framingham Heart Study (n = 5 209) (Schneider et al. 1980), 70 individuals acquired new RBBB in the follow-up. After the onset of RBBB, 6 % developed high-degree AV block – two of these had RBBB with LPFB, one had RBBB with LAFB and one RBBB without axis deviation. Throughout the entire period of 18 years of observation only 21 % remained free of clinically apparent CV diseases, and 30 % died of CV diseases within 10 years of the onset of RBBB. Incident bifascicular RBBB (with LAFB or LPFB) especially identified those most likely to have associated CV abnormalities. However, isolated RBBB *per se* was not associated with increased mortality after adjustment for CV comorbidity. In another study of the

same population (n = 1 759) (Dhingra et al. 2006), RBBB (n = 59) was not associated with a risk of new-onset heart failure.

In the Copenhagen City Heart Study (n = 18 441) (Bussink et al. 2013), RBBB (n = 166) was associated with increased risk of all-cause and CV mortality and myocardial infarction in subjects free from previous myocardial infarction and heart failure but the prevalence of a stable CHD in this cohort was not reported. RBBB was not associated with an increased risk of new-onset heart failure but possessed a risk for pacemaker implantation (6 % of patients with RBBB) during a median follow-up of 20.5 years. Similar results were obtained from the National Health and Nutrition Examination Survey (n = 8 527) (Badheka et al. 2013) as RBBB (overall n = 192; without CV disease n = 66) was associated with increased CV mortality in both individuals with or without CV disease (excluding hypertension and hypercholesterolemia) at the baseline. However, neither of these studies reported the prevalence of RBBB with bifascicular block pattern.

In the Women's Health Initiative study (n = 66 450) (Zhang et al. 2012), RBBB (overall n = 832; without CV disease n = 534) was associated with CV mortality only in women with a CV disease at the baseline (n = 52 663). In another study of the same cohort (Zhang et al. 2013) RBBB (n = 740) was not a predictor of incident heart failure even in women with a QRS duration ≥140 ms and RBBB. In the primary prevention study in Sweden (n = 7 392) of middle-aged men without history of myocardial infarction or stroke (Eriksson et al. 2005), RBBB (n = 70) was not associated with CV or all-cause death, but was associated with incidence of high-degree AV block and pacemaker implantation in asymptotic men. The rates of AV block and pacemaker implantation were only 4 % and 9 %, respectively, over 28 years.

In a large screening study of Irish Heart Foundation (Fahy et al. 1996), subjects with RBBB (n = 198) without apparent heart disease (self-reported) or hypertension had similar mortality rates as age- and sex-matched controls without bundle branch block at the baseline. In the Reykjavik Study (n = 18 762) (Thrainsdottir et al. 1993), RBBB (n = 79) was not a predictor of mortality neither in women nor men. In the Atherosclerosis Risk in Communities study (n = 15 408) (Zhang et al. 2016) during a mean 21 years of follow-up, RBBB (n = 181) was not associated with increased all-cause or CHD mortality even in the presence of QRS duration ≥140 ms with RBBB. Neither was bifascicular RBBB (n = 47; RBBB with LAFB or LPFB) associated with increased mortality. In another study of the same cohort (n = 14 478) (Zhang et al. 2015), bifascicular RBBB (n = 40) but not isolated RBBB (n = 159) with a QRS

duration <140 ms or ≥140 ms was associated with increased risk of novel heart failure.

In a study of adults referred for nuclear exercise testing to evaluate known or suspected coronary artery disease (n = 7 073) (Hesse et al. 2001), patients with RBBB (n = 190) displayed increased risk of death and similar mortality rates than those with LBBB. These patients had more often a priorly diagnosed CHD (67 %) than controls (55 %) or those with LBBB (59 %). In a recent study of patients without prior CV disease (n = 22 806) referred for exercise stress test at the Mayo Clinic in Rochester (Gaba et al. 2020), RBBB (n = 220) was predictive of CV and all-cause mortality. Patients with RBBB had lower exercise capacity, slower heart rate recovery, and more often need to stop the test because of dyspnoea, but had no more often a positive stress test than those without RBBB. Thus, even if counting on that the exercise stress test is accurate for detecting ischemia in the presence of RBBB, this intraventricular block could be a marker for underlying subclinical cardiac conditions, including diastolic dysfunction without symptomatic heart failure unrelated to CHD.

In patients aged ≥55 years with a stable CV disease (CHD and prior myocardial infarction were present in over 80 % and 50 % of the patients, respectively) or diabetes with ≥1 CV risk factor(s) but without heart failure (n = 9 541) (Sumner et al. 2009), neither prevalent (n = 428) nor incident (n = 168) RBBB were associated with mortality or risk of new-onset heart failure. Likewise, in a large study of patients with a stable CHD (n = 15 609) (Freedman et al. 1987), although RBBB (n = 250) was more often an indicator of a multivessel disease, it was not a predictor of mortality after adjustment for baseline variables.

Patients with masquerading bundle branch block consist a very high-risk subgroup with poor prognosis, related to the severe underlying disease (Elizari et al. 2013). An extremely high risk of a complete AV block (approximately 60 % in the work of Bayés de Luna (Bayés de Luna et al. 1988) and Gómez-Barrado (Gómez Barrado et al. 1997)), heart failure and mortality has been reported in these patients (Rosenbaum et al. 1968, Rosenbaum 1970, Bayés de Luna et al. 1988, Gómez Barrado et al. 1997).

2.4.1.1 Prognosis in Myocardial Infarction

Special attention should be paid in the presence of acute myocardial infarction with new or presumably new RBBB. Historically, the mortality in patients with RBBB and acute myocardial infarction reached 80 % before the thrombolytic era (Godman et

al. 1971, Gould et al. 1972). The development of RBBB in a setting of myocardial infarction is an independent marker of poor prognosis (Ricou et al. 1991), and RBBB was associated with both increased in-hospital and long-term mortality yet in the 21st century (n = 63 103) (Xiang et al. 2016). RBBB is often accompanied with LAFB in acute myocardial infarction as they both share the same blood supply (septal branch of the left anterior descending artery). In a Czech study (Widimsky et al. 2012) (n = 6 742), the overall prevalence of RBBB was 6.3 % (n = 427) in a setting of acute myocardial infarction – 3.2 % had RBBB with LAFB, 0.3 % had RBBB with LPFB and 2.8 % had isolated RBBB. Patients with new or presumably new RBBB had the highest in-hospital mortality (18.8 %) and had a high rate of cardiogenic shock (15.4 %) at admission. Special care in this study was taken to analyze the presence of ST-segment deviations in patients with RBBB – TIMI flow 0-2 was found in 67 % of the patients with RBBB but no ST-segment elevation. Alarmingly, in patients with acute left main occlusion (n = 35), the acute left main occlusion presented with RBBB without ST-segment elevation in 26 % of the patients. Previous reports have also presented high rates of RBBB in the presence of acute left main occlusion (approximately 37 – 60 % of the cases) (Kurisu et al. 2004, Hirano et al. 2006, Sakakura et al. 2008, Fiol et al. 2012). However, the literature is limited as such patients rarely make it alive to the emergency department.

2.4.1.2 Prognosis in Heart Failure

In a Canadian study of patients hospitalized for acute heart failure (n = 9 082) (Abdel-Qadir et al. 2011), RBBB (n = 651) was associated with a nonsignificant 10 % increase for mortality (95% confidence interval; 0.99–1.21; p = 0.084) after adjustment for left ventricular ejection fraction. In a report from Italian congestive heart failure database (n = 5 517) (Baldasseroni et al. 2003), mortality was similar with or without complete RBBB (n = 336). In a Detroit study of 2 907 consecutive patients admitted to Henry Ford Hospital Cardiac Intensive Care Unit for severe acute decompensated heart failure from 1990 to 1998 (McCullough et al. 2005), RBBB (n = 211) was associated with higher mortality after discharge. In a Spanish study of patients with chronic heart failure (n = 2 254) (Cinca et al. 2013), RBBB (n = 134) was associated with cardiac death and pump failure after adjustments for left ventricular function and mass. Although not significant, cardiac death and pump failure death tended to be higher in the RBBB than in the LBBB group.

In patients with impaired left ventricular systolic function, RBBB has been associated with increased mortality. In retrospective analysis from the Efficacy of

Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (n = 2 962), RBBB (n = 234) was associated with both increased mortality and the composite endpoint of CV death or hospitalization for heart failure. Interestingly, RBBB was associated with similar mortality rates as LBBB (Wang et al. 2008). In Israeli Heart Failure Survey (n = 1 888) (Barsheshet et al. 2011), RBBB (n = 193) was associated with increased mortality in patients with reduced left ventricular function and in a subgroup of patients with left ventricular ejection fraction <30 %, and to worse prognosis compared to LBBB in the four-year follow-up. No increased mortality was seen in patients with RBBB (n = 76) and preserved left ventricular function in the earlier report of the same cohort (n = 698) in the four-year follow-up (Barsheshet et al. 2008).

In the post hoc analysis from spironolactone for heart failure with preserved ejection fraction trial (n = 3 426) (Joseph et al. 2016), RBBB (n = 174) was associated with increased heart failure hospitalizations, and RBBB but not LBBB was associated with the primary outcome of composite endpoint of CV death or hospitalization for heart failure.

2.4.2 Cardiac Resynchronization Therapy

To date, there has been no randomized controlled trial to address the efficacy of CRT specifically in patients with non-LBBB QRS morphology. An individual patient meta-analysis (Cleland et al. 2013) of five CRT trials concluded that QRS duration is the single most powerful predictor of the effects of CRT on morbidity and mortality with robust evidence for benefit with QRS duration ≥140 ms. The QRS morphology did not provide additional information about clinical response in this analysis. In addition, in the post-hoc analysis of The Resynchronization–Defibrillation for Ambulatory Heart Failure Trial there was a benefit of CRT in patients without LBBB after 2 years when QRS duration was ≥160 ms but a trend towards possible harm in patients with QRS <160 ms (Birnie et al. 2013). This was not true in the original retrospective analysis of the largest single CRT study (Zareba et al. 2011) and in the follow-up report of this study as CRT was not associated with any clinical benefit and possibly with harm in patients without LBBB even in the subgroup of patients with QRS duration ≥150 ms and non-LBBB QRS morphology (Goldenberg et al. 2014). The lack of benefit from CRT in those with non-LBBB QRS morphology was shown in an another meta-analysis of five major CRT studies (Cunnington et al. 2015).

2.5 Non-specific Intraventricular Conduction Delay

In Eppinger's and Rothberger's experiments in dogs in 1909, the investigators were amazed to find that a greater amount of the free wall of the left ventricle could be destroyed with relatively little change in the ECG compared with the effect of small lesions in the region of the ventricular septum (Eppinger and Rothberger 1909). In 1917, Oppenheimer and Rothschild proposed that intraventricular conduction blocks should be subdivided into bundle branch blocks and peripheral blocks that interfere the conduction beyond the main branches of the bundle of His and widen the QRS duration beyond the normal 100 ms without typical features of bundle branch blocks. They named the latter block as "arborization block" (Oppenheimer and Rothschild 1917).

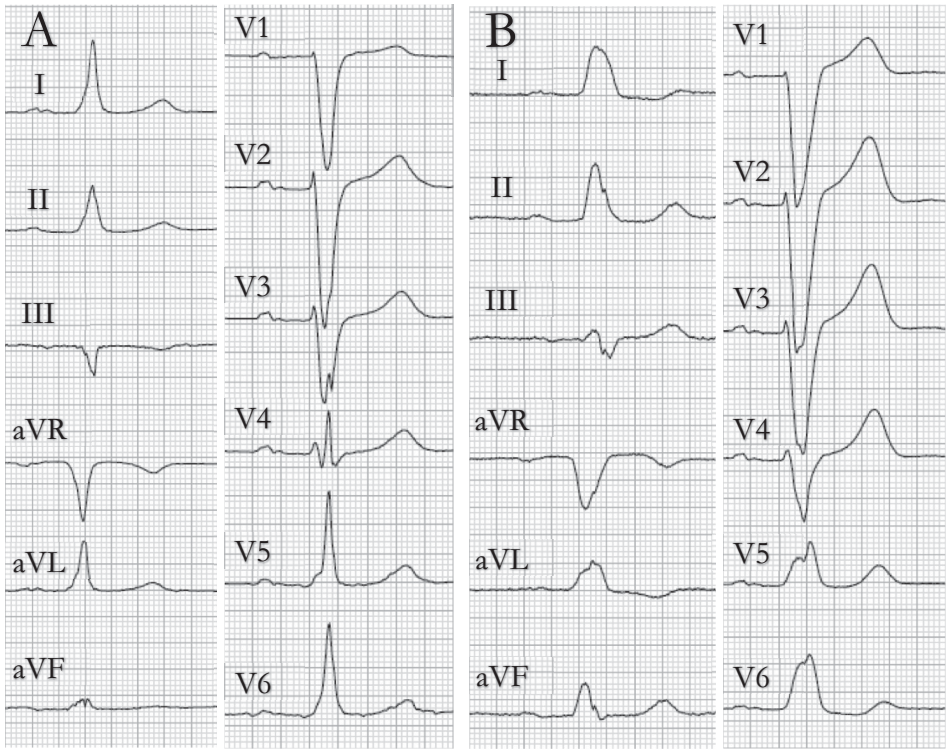
Non-specific IVCD is defined as a prolonged QRS duration neither fulfilling the criteria of LBBB nor RBBB (Figure 8). Thus, the definition of non-specific IVCD is influenced by the definition of LBBB. The American College of Cardiology and the American Heart Association defines the threshold for QRS duration greater than 110 ms (Surawicz et al. 2009) while the guidelines of the European Society of Cardiology use a more traditional cut-off value of ≥120 ms for non-specific IVCD (Brignole et al. 2013). While the guidelines of the American College of Cardiology and the American Heart Association state the definition may also be applied to a pattern with RBBB criteria in the precordial leads and LBBB criteria in the limb leads and vice versa (Surawicz et al. 2009), a masquerading bundle branch block (Rosenbaum et al. 1968, Rosenbaum 1970) should be considered in these cases and categorize the block after the main cause of the conduction delay, as RBBB.

Regional myocardial scarring as a result of fibrosis, previous myocardial infarction or LVH has been considered as pathophysiological background factors for the conduction delay. Term *intraventricular parietal block* (Alboni et al. 1976) has been applied in literature to intraventricular conduction disorders in which the affected site include Purkinje fiber network or pathologic hypertrophied or fibrotic myocardium, resulting in prolonged QRS duration (Eschalier et al. 2015). Term *peri-infarction block* can be applied when QRS complex is widened as a result of previous MI when there is a Q wave followed by a slowed and slurred R wave (Flowers et al. 1990). Increase in a QRS duration is only observed if the block is both significant and extensive (Eschalier et al. 2015).

In contrast to LBBB, subjects with non-specific IVCD show generalized slow conduction with less, but more heterogenous, dyssynchrony (Zareba et al. 2011) and considerable variation in the location of the latest activated site of the left ventricle

(Ploux et al. 2013). In earlier work, non-specific IVCD (n = 38) was a highly specific indicator of left ventricular dysfunction (Murkofsky et al. 1998). In the Framingham Heart Study population free of prior myocardial infarction and heart failure (Dhingra et al. 2005), increasing QRS duration without bundle branch block pattern also was positively related to left ventricular mass and dimensions measured by echocardiography in men and women.

Figure 8. A) Non-specific Intraventricular Conduction Delay. QRS duration is 134 ms without meeting the criteria of right or left bundle branch block (LBBB).
B) ECG of the same patient six months later with the development of LBBB. In addition to increased QRS duration (150 ms), there is a distinct change in the QRS morphology with mid-QRS notching.



In general population, the prevalence of non-specific IVCD has been estimated 0.2 – 1.7 % (Desai et al. 2006, Aro et al. 2011, Zhang et al. 2012, 2016, Badheka et al. 2013) and strongly associated with male sex (Desai et al. 2006, Aro et al. 2011, Badheka et al. 2013). Estimates of CHD in individuals with non-specific IVCD have varied from 0.2 to 60 % (Aro et al. 2011, Kurl et al. 2012, Zhang et al. 2012, Badheka et al. 2013). Likewise, the rate of prior myocardial infarction in subjects with non-

specific IVCD has been approximately 0 % to 30 % in previous studies (Desai et al. 2006, Aro et al. 2011, Kurl et al. 2012).

In the general heart failure population, the prevalence of non-specific IVCD has been reported around 4 – 6 % (Baldasseroni et al. 2003, Sandhu and Bahler 2004, Abdel-Qadir et al. 2011, Cinca et al. 2013). Ischemic etiology is more frequent than dilated cardiomyopathy in these patients. In a recent study combining clinical data from two large trials investigating patients with heart failure with reduced ejection fraction (n = 11 861), ischemic etiology was present in 63 % of the patients with non-specific IVCD (Kristensen et al. 2020). In line, ischemic etiology was present in half of the patients and dilated cardiomyopathy in one third of the patients with non-specific IVCD in a study from the Italian congestive heart failure database (Baldasseroni et al. 2003). In patients with autopsy-proven dilated cardiomyopathy, non-specific IVCD was present in 26 % of cases (Wilensky et al. 1988).

2.5.1 Prognostic Implications

In 1917, Oppenheimer and Rothschild observed 58 patients with "arborization" block. The prognosis was considered very serious – the mortality was approximately 50 % within two years. In the Finnish cohort of ≥ 65-year-old subjects (n = 697) of the Seven Countries study (Tervahauta et al. 1996), 5-year mortality was 25% (2/8 subjects) for non-specific IVCD. Data were collected during the 1980s, and, in general, mortality figures were high. Another study (Desai et al. 2006) found a continuous relation between QRS duration and mortality in a general medical population (n = 46 933) as every 10 ms increase in QRS duration without bundle branch block increased CV risk by 18 %, and 31 % of patients with a QRS duration ≥120 ms without LBBB or RBBB died during a mean follow-up of six years.

In a Finnish Coronary Heart Disease Study (n = 10 899) (Aro et al. 2011), non-specific IVCD (n = 67; defined by the American guidelines (Surawicz et al. 2009) i.e. QRS duration ≥110 ms) predicted increased overall and CV mortality and the risk of arrhythmic death. Excluding subjects with any suspected heart disease did not have impact on the results. In another Finnish cohort of men aged 42 to 60 years with a 19-year follow-up (n = 2 049) (Kurl et al. 2012), QRS duration ≥110 ms without bundle branch block was an independent predictor of sudden cardiac death even after men with prior myocardial infarction were excluded. This was also true in the Framingham Heart Study population (Kreger et al. 1987) as non-specific IVCD was associated with increased risk of sudden death, and in a subgroup of patients

with a known ischemic heart disease in the Oregon Sudden Unexpected Death Study (overall n = 848; non-specific IVCD n = 118) (Teodorescu et al. 2011).

In the National Health and Nutrition Examination Survey (n = 8 527) (Badheka et al. 2013) non-specific IVCD (overall n = 352; without CV disease n = 116) was associated with a 40 % increase of CV death but this was not statistically significant (P = 0.09). Likewise, non-specific IVCD was associated with a 50 % increase of CV death in individuals without CV disease at the baseline but, again, the result was not statistically significant (P = 0.30).

In the Atherosclerosis Risk in Communities study (n = 15 408) (Zhang et al. 2016) during a mean 21 years of follow-up, non-specific IVCD (n = 111) was associated with increased all-cause and CHD mortality. In addition, a QRS duration 100 – 109 ms was associated with increased CHD mortality, and QRS duration 110 – 119 ms was associated with both increased CHD and all-cause mortality as compared to those participants with QRS duration <100 ms. In these subjects, ECG evidence of previous myocardial infarction and LVH together accounted for 48 % of all the CHD deaths for 31 % of all-cause mortality. In another study of the same cohort (n = 14 478) (Zhang et al. 2015), non-specific IVCD (n = 103) was associated with increased risk of novel heart failure.

In the Women's Health Initiative study (n = 66 450) (Zhang et al. 2012), non-specific IVCD (overall n = 122; without CV disease n = 49) was associated with CHD death and all-cause mortality only in women with a CV disease at baseline (n = 52 663). However, in another study of the same cohort (n = 65 975) (Zhang et al. 2013), non-specific IVCD (n = 117) was a predictor of incident heart failure after excluding patients with prevalent heart failure (self-reported).

In another study of the Framingham Heart Study population (Dhingra et al. 2006), after excluding individuals with prevalent heart failure or previous myocardial infarction (n = 1 759), non-specific IVCD (n = 28) was associated with a two-fold risk of new-onset heart failure in the subjects with this conduction disorder in the baseline ECG in early 1980s.

In a large retrospective cohort study of primary care patients referred for ECG in Copenhagen (Rasmussen et al. 2019), non-specific IVCD (n = 3 050) alongside with LBBB (n = 1 037) and RBBB (n = 3 510) was associated with an increased risk of future pacemaker implantation in both sexes. The 10-year risk of pacemaker implantation was highest in individuals aged 70 – 89 years with the absolute risk value ranging from 9 % to 10 % in females and 11 % to 14 % in males for each block. Of note, none of the blocks predicted the incidence of atrial fibrillation.

2.5.1.1 Prognosis in Heart Failure

In patients with heart failure, non-specific IVCD has been associated with increased mortality and poor prognosis (Kashani and Barold 2005, Wang et al. 2008). In the Swedish Heart Registry study (n = 25 171) (Lund et al. 2013), QRS prolongation was harmful and the excess risk of mortality was independent of the presence of LBBB. In a large study of patients with heart failure with reduced ejection fraction (n = 11 861), those with non-specific IVCD (n = 454) had an increased risk of all-cause and CV mortality, and higher rates of heart failure hospitalizations and pump failure deaths than those with a QRS duration <110 ms (Kristensen et al. 2020). In a retrospective analysis from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan cohort (n = 2 962) (Wang et al. 2008), non-specific IVCD (n = 178) was associated with increased mortality and hospitalization for heart failure and yielded similar prognosis as LBBB.

However, in a report from Italian congestive heart failure database (n = 5 517) (Baldasseroni et al. 2003), the mortality was similar in patients with or without non-specific IVCD (n = 339). In the post hoc analysis from the treatment of preserved heart failure with an aldosterone antagonist trial (n = 3 426) (Joseph et al. 2016), non-specific IVCD (n = 160) was associated with increased CV and overall mortality and heart failure hospitalizations, but the risk was attenuated after adjustment for age, sex and ejection fraction.

In patients with a history of CHD with depressed left ventricular function and a documented nonsustained ventricular tachycardia (n = 1 638) (Zimetbaum et al. 2004), non-specific IVCD (n = 294) was associated with a 50 % increase of arrhythmic death and total mortality.

2.5.2 Cardiac Resynchronization Therapy

It is observed that patients with non-specific IVCD have shorter QRS duration than those with LBBB, which may account for the lack of benefit observed in these patients. Earlier, it was reasoned that as there are patients with severe heart failure with reduced ejection fraction and QRS duration <120 – 130 ms but with echocardiographic evidence of left ventricular dyssynchrony, these patients might benefit from CRT. However, a large randomized clinical trial was stopped for futility on the recommendation of the data and safety monitoring board as CRT did not reduce the rate of death or hospitalization for heart failure and may increase mortality in these patients (Ruschitzka et al. 2013).

2.6 Left Anterior Fascicular Block

Anatomically, the left anterior fascicle is thinner and longer compared to the posterior fascicle. The left anterior fascicle receives its blood supply from the first major septal branch of the left anterior descending coronary artery. It is located beneath the left ventricle outflow tract, in a vulnerable and turbulent region of the left ventricle (Elizari et al. 2007) and is directed to the anterolateral papillary muscle. Indeed, processes that involve the anterior wall of the interventricular septum, the outflow tract of the left ventricle or the anterolateral wall may injure the anterior fascicle. They include hypertensive and ischemic heart diseases, which also account for the majority of cases of LAFB, aortic valve diseases and cardiomyopathies. In the Rosenbaum's original work, CHD was present in 41 % of clinical cases of this conduction disturbance. As with other conduction blocks, primary conduction diseases (Lenègre's and Lev's diseases) may impair the conduction in the left anterior fascicle (Rosenbaum et al. 1968, Rosenbaum 1970). In patients with fully developed Chagas cardiomyopathy, LAFB occurs in 50 to 80 % of the cases (Rosenbaum 1969).

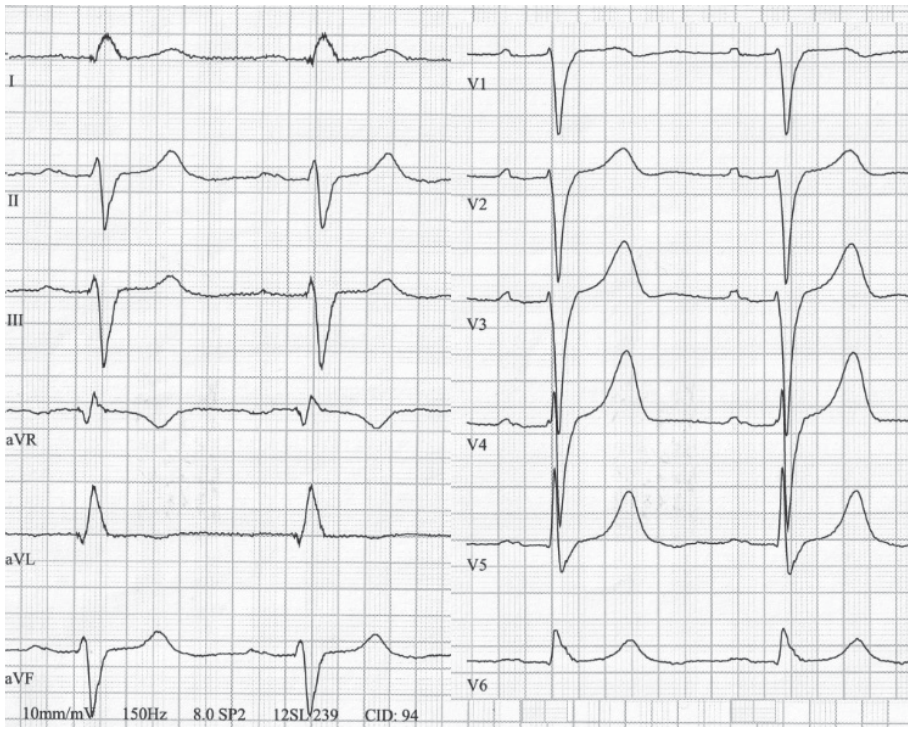
In LAFB (Figure 9), three major changes in the QRS morphology can be noted. Firstly, small Q waves in leads I and aVL appear as a result of rightward shift of the initial QRS forces. Secondly, deep S waves emerge in inferior leads II, III and aVF with S wave in lead III deeper than in lead II, and R wave in inferior leads is always observed in a typical LAFB. Finally, QRS axis shifts $\leq -45°$ as a result of the shift in the main QRS forces superiorly and to the left (Rosenbaum et al. 1968, Rosenbaum 1970). However, the criteria for required amount of axis deviation is arbitrary as small degrees of block in the anterior division of the left bundle branch may totally overlap with normal variants. As an example, QRS axis shift in successive tracings may show electrical axis at +50°, +40°, +30°, and 0° covering the whole range up to −45°, making the diagnosis of incomplete to complete block in the anterior division of the left bundle branch. Thus as it is impossible to tell when a partial or incomplete LAFB is present it has been suggested that the limit be set at −45°, which seems to be the best dividing line between LAFB and left axis deviation because of other clinical conditions (Elizari and Chiale 2012). In LAFB, precordial leads V2 and V3 may show poor R wave progression or even small anterior Q waves imitating old anteroseptal infarction as a result of early activation of the posterior wall of the left ventricle (Elizari et al. 2013), while leads V5 and V6 may record deeper S waves (Elizari et al. 2007). It should be noted that characteristics in the precordial leads are vulnerable to placement of the electrodes as well as to individual variations in the position of the heart (Elizari et al. 2007).

It is not uncommon that LAFB may pose diagnostic problems in clinical practice. LAFB may both simulate and conceal myocardial infarction and LVH. While it is not typical of LAFB to conceal extensive necrosis, a more localized myocardial damage can be obscured. As discussed above, LAFB may express precordial Q waves imitating anteroseptal myocardial infarction; if these Q waves disappear in leads V2 and V3 recorded one intercostal space below the conventional level, they are more likely a result of LAFB and not of myocardial infarction (Elizari et al. 2007, 2013). If inferior myocardial infarction spares the areas of the left ventricle supplied by posterior fascicle the infarction may be concealed. Tiny Q wave in lead II before the initial R wave or a notched R wave or R wave voltage in lead II lower than in lead III is not observed in typical LAFB and is a sign of inferior fibrosis or necrosis. Qr pattern instead of QS pattern in lead II can be seen when extensive infarction mimics LAFB. When inferior infarct and LAFB coexist, there can be QS pattern in lead II. This diagnosis is strongly supported if deep SII and SIII waves are present because pure inferior infarction tends to produce low voltage in the QS complexes of leads II and III. Furthermore, inferior infarction can even diminish both the initial R waves in inferior leads and the small Q wave in lead I even in the presence of LAFB (Rosenbaum and Elizari 1973). LAFB may simulate LVH in limb leads I and aVL and conversely conceal LVH in left precordial leads (Elizari et al. 2007). LAFB may even produce signs of left ventricular "strain" pattern in a form of secondary repolarization abnormalities (Rosenbaum 1969). RBBB with concomitant LAFB may mimic and lead to false diagnosis of LBBB, referred as *masquerading bundle branch block* (Rosenbaum et al. 1973). Some overlap between left axis deviation and LAFB is unavoidable, and an isolated left axis deviation is a common, age-associated ECG finding without adverse prognosis (Ostrander 1971).

Considering the anatomic relations, it is not surprising that a block in the anterior left fascicle is more common than a block in the posterior fascicle. The prevalence of LAFB in the original work of Rosenbaum et al. was reported to be 4.6 % (76 of 1 658 patients) (Rosenbaum 1970). The reported prevalence of LAFB in the literature has been 0.9 to 6.4 % (Rotman and Triebwasser 1975, Corne et al. 1978, Elizari et al. 2007, Haataja et al. 2013), though the unavoidable overlap with left axis deviation and studied patient population may explain the differences in prevalence. The prevalence of LAFB has been shown to increase with age (Corne et al. 1978, Haataja et al. 2013, Yiheng et al. 2016).

In the general heart failure population, the prevalence of isolated LAFB was reported around 9 % (Cinca et al. 2013).

Figure 9. Left Anterior Fascicular Block.



2.6.1 Prognostic Implications

In studies from 1960s and 1970s (Rosenbaum et al. 1968, Yano et al. 1975), LAFB was not associated with excessive mortality in the general population. In a population of clinically healthy Japanese American men (n = 8 000), those with LAFB (n = 70) displayed no increased mortality (Yano et al. 1975). This was also true in a more recent Kailuan study (overall n = 101 510; LAFB n = 661) (Yiheng et al. 2016).

In a large study of primary care patients (n = 227 543) without a history of atrial fibrillation, hypertension, diabetes, myocardial infarction, structural heart disease, or heart failure (Nielsen et al. 2014), those with LAFB (n = 3 572) had a 13 % increased risk of overall mortality but were not in a risk of future CV events in the median follow-up of 6 years. In the Cardiovascular Health Study of subjects 65 or older without a CV disease at the baseline (n = 1 664), those with LAFB (n = 39) had an increased risk of all-cause and CV mortality, atrial fibrillation, and congestive heart failure in a median follow-up time of 16 years. Through 10 years of annual ECGs, only four (10 %) individuals with LAFB developed RBBB (Mandyam et al. 2013).

In a retrospective autopsy study (n = 570) (Ding et al. 2018), LAFB (n = 92) was not an independent relevant factor for the occurrence of CHD, but the cases with LAFB had more pathological CHD and more often signs of prior myocardial infarction. The presence of LAFB lowered the accuracy to clinically diagnose CHD. Furthermore, those with LAFB had increased all-cause and CV mortality.

In a setting of acute myocardial infarction, the presence of a new or presumably new LAFB strongly supports a culprit artery location in the proximal left anterior descending in anterior ST-segment elevation myocardial infarction, while in the presence of occlusion of right coronary artery or left circumflex the development of LAFB indicates a concomitant significant stenosis of left anterior descending artery before the first septal branch (Nikus et al. 2020). In a study of patients with acute coronary syndrome (n = 11 820) (Zhang et al. 2014), patients with isolated LAFB (n = 692) were associated with worse Killip class and higher GRACE risk score, but after adjustment for clinical characteristics isolated LAFB was not an independent predictor of in-hospital and 6-month mortality and did not carry incremental prognostic value beyond the known prognosticators in the GRACE risk models.

In the Women's Health Initiative study (n = 66 450), prognostic implications of isolated LAFB were not reported. The combination of RBBB with LAFB (overall n = 71; without CV disease n = 40) was associated with CHD death and all-cause mortality only in women with a CV disease at baseline (n = 52 663) (Zhang et al. 2012). In another study of the same cohort (n = 65 975) (Zhang et al. 2013), the combination of RBBB and LAFB (n = 139) was a predictor of incident heart failure.

In patients with suspected CHD and no history of myocardial infarction referred for dobutamine stress echocardiography (n = 1 187) (Biagini et al. 2005), ischemia occurred more frequently in patients with LAFB (n = 159), and LAFB was associated with increased CV mortality during a mean follow-up of 5 years whether the stress test was positive or not. However, those with LAFB had twice more often a history of heart failure than those without. In another study of patients undergoing stress echocardiography for suspected CHD (n = 1 230) (Cortigiani et al. 2003), isolated LAFB (n = 106) was not associated with mortality, but the combination of RBBB and LAFB (n = 44) was an independent predictor of mortality. Among patients without stress-induced ischemia (n = 980), survival was again worse for patients with RBBB and LAFB (n = 32). Of note, isolated RBBB and LBBB were not associated with worse outcome in this study.

In a Spanish study of patients with chronic heart failure (n = 2 254), isolated LAFB (n = 154) was not associated with cardiac mortality or death due to pump failure after adjustment for left ventricular function and therapy (Cinca et al. 2013).

2.7 Left Posterior Fascicular Block

Isolated LPFB is the rarest of all intraventricular conduction blocks (Pérez-Riera et al. 2018), and in most cases, LPFB is accompanied by RBBB as a bifascicular block (Elizari et al. 2007). In fact, even Rosenbaum himself hadn't seen a pure isolated chronic LPFB at the time of "Los Hemibloques" (Rosenbaum 1969). Anatomically, located in the inflow tract of the left ventricle and directed to the posteromedial papillary muscle, left posterior fascicle is shorter and thicker than the anterior fascicle. In addition, left posterior fascicle has a dual arterial blood supply as both left anterior descending and right coronary artery gives off branches to perfuse the posterior fascicle. In the left-dominant circulation, the posterior fascicle is supplied by the left anterior descending artery and the posterior descending artery of the left circumflex artery. Combining the previous, it is not unpredictable that the left posterior fascicle is the least vulnerable segment of the whole conduction system, and why LPFB occurs a lot less frequently in hypertensive heart disease and ventricular dilation than LAFB (Rosenbaum 1968).

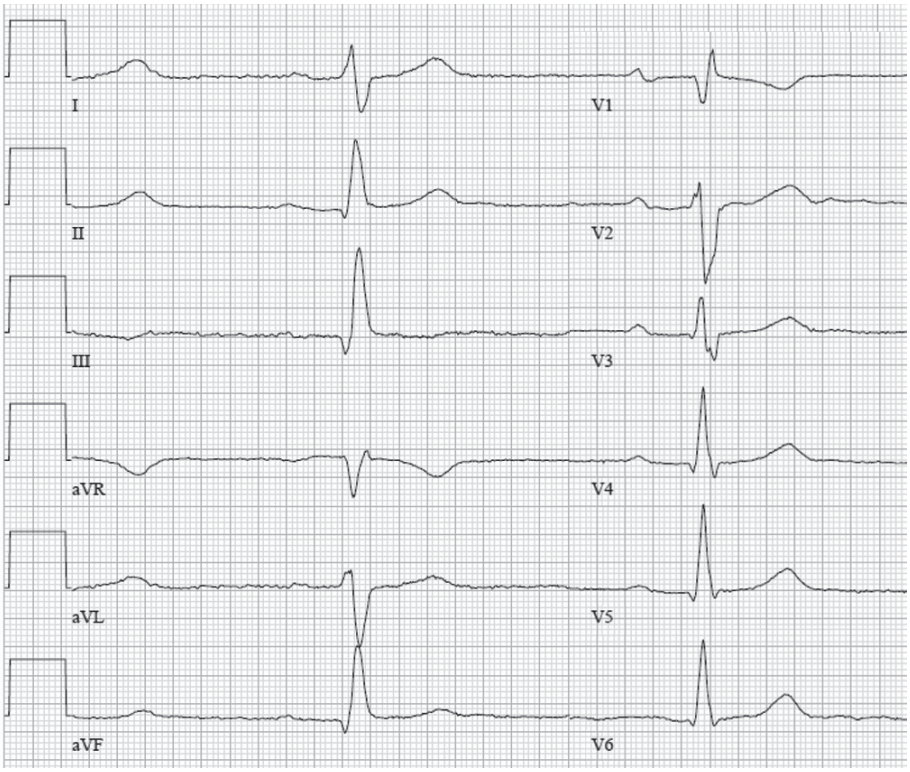
In LPFB (Figure 10), three major changes in the QRS morphology can be noted: Firstly, small Q waves in inferior leads as a result of leftward and superior shift of the initial QRS forces. Secondly, SIQIII pattern in the limb leads and rS pattern in leads I and aVL. Finally, QRS axis shifts >100° as a result of the shift in main QRS forces. As a matter of fact, in many cases the changes provoked by conduction delay in the left posterior division may be so trivial that the diagnosis can only be made by comparison with the previous recordings (Elizari and Chiale 2012).

The diagnosis of LPFB should always consider the clinical aspects. Definite diagnosis cannot be made in the presence of right ventricular hypertrophy, emphysema with or without chronic obstructive pulmonary disease, previous large lateral myocardial infarction or extremely vertical heart as a normal variant (Elizari et al. 2007, Pérez-Riera et al. 2018). Accordingly, R wave should be higher in lead III than in lead II in a true LPFB (Pérez-Riera et al. 2018). Thus, it is always difficult and challenging to recognize and to make the diagnosis of LPFB from one single tracing without clinical information. As stated by Rosenbaum, pure LPFB is electrocardiographically "colorless, deceptive, and non-specific" (Rosenbaum et al. 1968, Rosenbaum 1970).

LPFB may conceal the signs of previous inferior myocardial infarction (Godat and Gertsch 1993, Elizari et al. 2007) due to inferior and rightward shift of the main QRS forces, eliminating inferior Q waves and producing tall R waves instead.

In general population, the prevalence of LPFB has been reported around 0.1 % (Haataja et al. 2013). In a Swiss study of ECGs recorded in the department of Cardiology or Internal Medicine in 1991 (Godat and Gertsch 1993), isolated LPFB was found in 0.24 % of 2 502 ECGs. In a study of French aircrew members examined for fitness assessment (n = 69 186) (Monin et al. 2016) with mean age of 32 and 28 years for males and females respectively, the overall prevalence of LPFB (n = 66) was 0.1 % in this generally extremely healthy population. However, this may be an overestimation as the required QRS axis deviation was only ≥90° in this study.

Figure 10. Left Posterior Fascicular Block.



The prevalence of RBBB with LPFB has been less than 0.1 % and approximately 2 to 5 % of all RBBBs in the Western general population studies (Rotman and Triebwasser 1975, Schneider et al. 1980, Eriksson et al. 1998). In a study from 1975, the most frequent etiology for chronic RBBB with LPFB was hypertensive heart disease (in approximately 50 % of patients), while one third had primary conduction disease (Dhingra et al. 1975). Studies from 1970s reported the prevalence of CHD being 19 – 44 % in these patients (Rosenbaum 1970, Dhingra et al. 1975). In the

Framingham Heart Study (Schneider et al. 1980), three of four incident cases of RBBB with LPFB had CHD and two of four had congestive heart failure – half of the patients died due to CV causes.

2.7.1 Prognostic Implications

Given to the rarity of isolated LPFB, studies evaluating the prognostic implications of this type of block are practically non-existent.

In previous study of the Health 2000 sample (n = 6 299) (Haataja et al. 2015), isolated LPFB (n = 8) was neither associated with overt CV diseases nor mortality. The lack of patients with this type of block prohibit to draw any definite conclusions.

In the Women's Health Initiative Study (n = 65 975) (Zhang et al. 2013), only one of the patients with chronic RBBB and LPFB (n = 22) developed incident heart failure during an average follow-up of 14 years.

Considering the anatomic characteristics, Rosenbaum and colleagues noted that a conduction disturbance in the thick posterior fascicle is often a sign of concomitant involvement of the left anterior fascicle or the right bundle branch or both as a true trifascicular disease of the conduction system (Rosenbaum et al. 1968, Rosenbaum 1970). This is because the lesions are so widespread in the whole heart or in the conduction system that the right bundle branch and the anterior division of the left bundle branch are usually damaged too (Rosenbaum 1968). Supporting this, the authors noted that when RBBB was present with LPFB, there was also a direct evidence of LAFB in one quarter of the patients and the PR interval was prolonged in 90 % of the patients (incomplete trifascicular block). In their work, 83 % of the patients with a bifascicular disease of RBBB with LPFB developed AV conduction disturbances and approximately 60 % developed a high-degree AV block with Stokes-Adams attack over an unspecified follow-up period. The rate is extremely high compared to patients with RBBB and LAFB as a high-degree AV block developed in 17 % of these cases over many years. However, in a prospective study (Dhingra et al. 1975) with 21 patients with chronic RBBB and LPFB, only two patients developed a high-degree AV block during a mean follow-up of 1.8 years.

Differences in study populations and follow-up period may to some extent explain the diverging results from these two studies. In another study from 1970s with 15 patients with RBBB and LPFB (Narula and Samet 1971), the HV interval was prolonged in 80 % of the patients, compared to 29 % in the work of Dhingra et al. While the authors concluded that the true incidence of progression to a high-

degree AV block has probably been previously overestimated, a high proportion of patients (35 %) had Chagas' disease in Rosenbaum's work, known to produce widespread involvement of the conduction system and worse prognosis in those with a bifascicular block (Rosenbaum 1964).

In a retrospective study of patients with a history of syncope and chronic bundle branch block referred to electrophysiologic study (n = 171) (Boule et al. 2014), patients with bifascicular block pattern of RBBB with LPFB (n = 14) were strongly associated with the presence of advanced His-Purkinje conduction disturbances (11 out of 14 patients) in the electrophysiological study, whereas RBBB with LAFB (n = 66) was not. Furthermore, the presence of incomplete trifascicular block pattern of 1st degree AV block and RBBB with LPFB (n = 9) carried a particularly high risk – in fact, 8 out of 9 patients received pacemaker shortly and the only one with normal electrophysiological study required pacemaker implantation two years later after a spontaneous episode of 3rd degree AV block. Thus, a syncopal episode may indicate a higher risk of AV block in these patients. Anecdotally, a high rate of syncope in the study of Rosenbaum (50 % of patients) compared to work of Dhingra (15 %) may well explain the differences in the clinical course of these studies.

In a study from 1970s (Rizzon et al. 1975), the appearance of isolated LPFB in acute myocardial infarction was a marker of poor prognosis – in-hospital mortality was 80 %. Likewise, progression to complete AV block was considerable (40 %) and 80 % died of pump failure. As left posterior fascicle is perfused by both left anterior and posterior descending arteries, a severe two-vessel disease should typically be present for a new LPFB to develop in a setting of acute myocardial infarction. Not surprisingly, in most cases there was evidence of infarction involving both the anterior and inferior ventricular walls of the left ventricle (Rizzon et al. 1975).

In the prethrombolytic era, appearance of RBBB with LPFB in acute myocardial infarction was a sign of extremely poor prognosis – in a previous study, in-hospital mortality was 100 % and death was either from cardiogenic shock, complete AV block or ventricular fibrillation (Rizzon et al. 1975). Three other studies from 1970s established that the mortality in these patients was 33 – 80 % (Scanlon et al. 1970, Godman et al. 1971, Scheinman and Brenman 1972). Taken all these studies together, in-hospital mortality in patients with acute myocardial infarction with RBBB and LPFB (n = 40) was 75 % and the rate of complete AV block was 30 %.

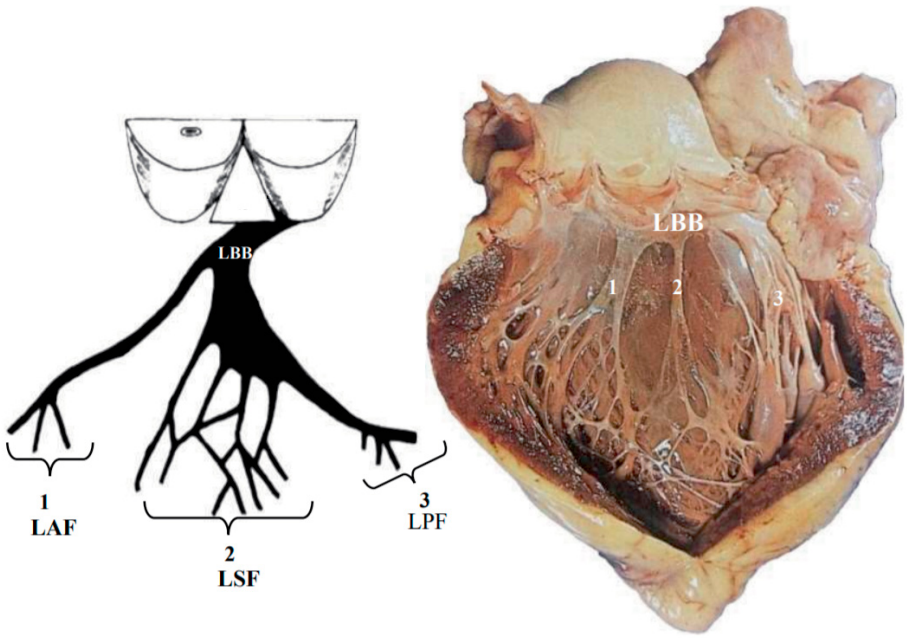
Even in the modern era of primary percutaneous coronary intervention in acute myocardial infarction, RBBB with LPFB is a hallmark of poor prognosis – this type of block carried the highest in-hospital mortality (18 %) in a Czech study from 2012 (Widimsky et al. 2012).

2.8 Left Septal Fascicular Block

In 1968, Rosenbaum, Elizari and Lázzari considered the human left infra-Hisian system bifascicular as anatomically and functionally in their classical reviews (Rosenbaum et al. 1968, Rosenbaum 1970). Later, Elizari pointed out that the existence (Figure 11), functional and, probably, clinical significance of the middle septal fibers cannot be totally disregarded (Elizari et al. 2007).

In 1970, Durrer demonstrated in his classical work that three endocardial regions activate simultaneously in the human left ventricle, corresponding roughly to the myocardial insertions of the three fascicles of the left bundle branch. The septal activation started in the middle third of the interventricular septum at the end of the left septal fascicle (Durrer et al. 1970).

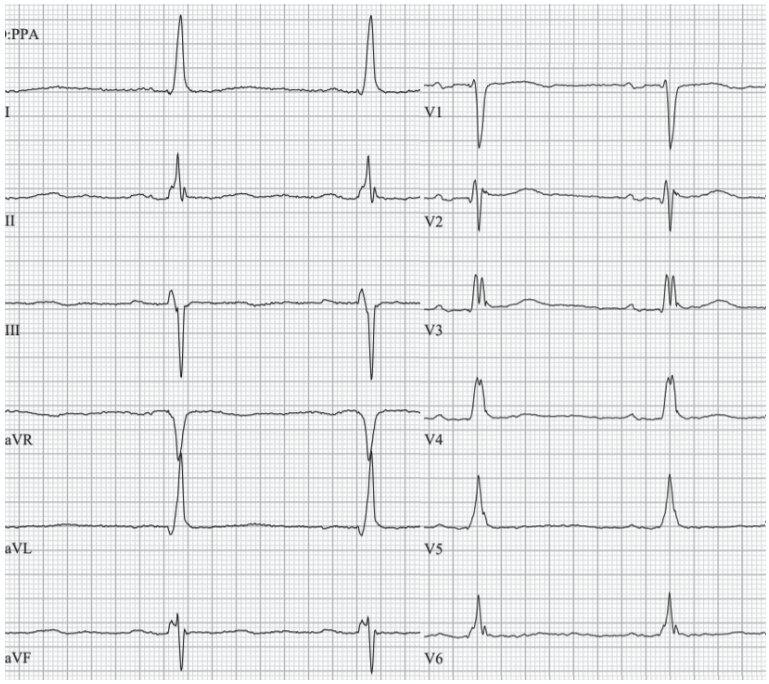
Figure 11. Anatomy of the Left Conduction Pathways.
LAF = Left Anterior Fascicle; LBB = Left Bundle Branch; LPF = Left Posterior Fascicle; LSF = Left Septal Fascicle. Reprinted with permission from Pérez-Riera.



In 1970, Medrano suggested that the "atypical" pattern of LBBB with Q waves in left lateral lead aVL may be explained by the preserved activation of the left septal fibers (Medrano et al. 1970). In 1976, Hoffman suggested that a conduction delay in the middle septal fibers is characterized by prominent anterior forces in lead V2 and

occasionally in lead V1 (Hoffman et al. 1976). The anterior shift of the QRS loop in horizontal plane was seen in the earlier work of Uhley in 1964 after the experimental section of the middle septal fibers (Uhley and Rivkin 1964). More recently, in 2001, Sanches, Moffa and Sosa performed biventricular endocardial catheter mapping in five patients meeting ECG criteria for left septal fascicular block (LSFB) (Sanches et al. 2001). These ECGs were characterized by prominent anterior forces and absence of Q waves in left lateral leads I and V5-V6. The authors observed a conduction delay in the middle septal surface – corresponding to the area of distribution of the septal fibers (Pérez-Riera et al. 2008).

Figure 12. The baseline ECG of the same subject as in Figure 13 without prominent anterior forces (without LSFB).



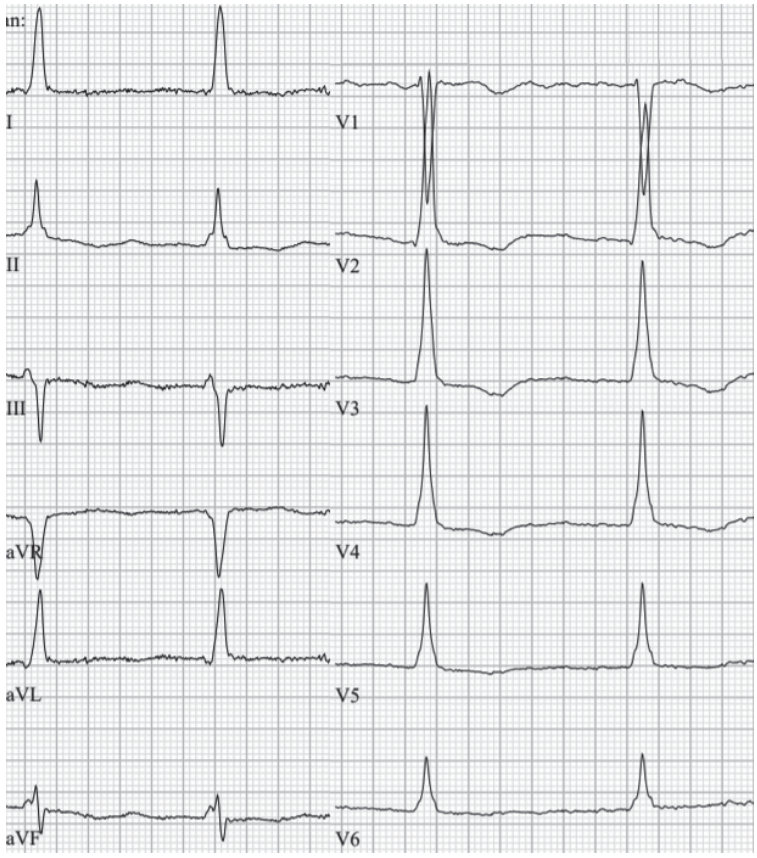
The anatomy of the left septal fascicle, in cases it exists as a distinct entity, is considerably more variable than the other two branches of the left His system (MacAlpin 2002) with abundant interconnections. In 1972, Demoulin and Kulbertus presented their classical histopathologic study of the anatomy of the left bundle branch (Demoulin and Kulbertus 1972). In 11 out of 20 cases, the left bundle branch gave off a third radiation. These fibers emerged from the predivisional left main truncus in 5 cases or from the anterior or posterior fascicle in 3 cases each and travelled to the midseptal area forming a fan-like network (Figure 2 on page 26).

Three years later, Kulbertus showed in his histopathological work with 49 human hearts that in only 15 % of them the third fascicle was missing (Kulbertus 1975).

Different criteria for LSFB has been proposed on the basis of anecdotal reports (Gambetta and Childers 1973), results of experimental incision of the septal fibers in canines (Uhley and Rivkin 1964), and computer-based models (MacAlpin 2002). Thus, the task force of the American College of Cardiology and the American Heart Association (Surawicz et al. 2009) do not recommended the use of term septal fascicular block as there are no universally accepted criteria.

In the review of Pérez-Riera in 2011, the author proposed ECG criteria for LSFB based on the literature (Pérez Riera et al. 2011). The major criterion for the left septal block is the presence of transient prominent anterior forces (Figure 13). That is, an intermittent or transient increment in R wave voltage in the right precordial leads. This manifests as R/S ratio >2 in V1 with R wave height ≥5 mm, or as R/S ratio >2 in V2 with R wave height ≥15 mm or S wave <5 mm (Mori et al. 1992).

Figure 13. Left Septal Fascicular Block. Transient prominent anterior forces are now present.



The left septal fascicle is exclusively supplied by septal branches of the left anterior descending artery. Not surprisingly, a critical lesion of the left anterior descending artery may produce a pattern of LSFB (Uchida et al. 2006, Pérez-Riera et al. 2015).

In 2014, the first case report of a rate-related (phase 4 or bradycardia-depended) LSFB was published (Ibarrola et al. 2014).

Differential diagnosis for LSFB includes all other possible etiologies of prominent anterior forces, including pre-excitation (Wolff-Parkinson-White type A), previous lateral (formerly posterior) myocardial infarction, RBBB, right ventricular hypertrophy, hypertrophic obstructive cardiomyopathy, precordial lead misplacement, and a normal variant. Thus, the diagnosis should always consider the clinical aspects.

However, controversies remain. In 2012, a consensus article by Bayés de Luna, Pérez-Riera, Elizari, and others ended up with discrepancies (Bayés de Luna et al. 2012b). In 1978, Reiffel and Bigger published two cases of aberrancy with prominent anterior forces which seemed independent of RBBB (Reiffel and Bigger Jr 1978). Yet, their pattern resembles a pattern of progressive RBBB very similar to the one published by Piccolo (Piccolo et al. 1980), though the lack of Q waves may be explained by a left conduction defect. The progressive pattern of RBBB with prominent anterior forces was seen to be very similar that appears after "touching" the right bundle with a catheter (Peñaloza et al. 1961). Thus, a predivisional first-degree conduction disorder in the right bundle branch may manifest with an anterior RS pattern before the appearance of r' in V1 (Bayés de Luna et al. 2012b). In the work of Uhley (Uhley and Rivkin 1964) the anterior shift of the QRS forces was not uniform, and Dabrowska (Dabrowska et al. 1978) described the lack of septal Q wave after cutting the middle fibers. MacAlpin (MacAlpin 2002) emphasized in his review that LSFB is characterized by the loss of left lateral Q waves. However, his examples of lack of these septal Q waves could also be explained by a predivisional first-degree LBBB (Bayés de Luna et al. 2012b).

The lack of uniform pattern of LSFB could be explained by the great individual variety in the left septal fiber network as observed in the histopathologic studies of Demoulin (Demoulin and Kulbertus 1972) and Kulbertus (Kulbertus 1975). In conclusion, while the experimental evidence demonstrates that a block in the middle septal fibers may produce ECG changes, further studies are needed.

The prevalence of LSFB in a general population is not known as there are no published reports to date. It has been supposed the septal block is far more common than isolated LPFB. In 1992, using the diagnostic criteria previously presented for prominent anterior forces in absence of other possible etiologies, Mori found out

the prevalence of LSFB was 3.5 % among hospitalized subjects, mainly consisting of elderly patients (Mori et al. 1992). In 2002, MacAlpin reviewed approximately 26 000 consecutive ECGs processed in the ECG laboratory in California to identify those meeting various criteria for LSFB derived from the literature, mainly by the lack of left lateral Q waves in absence of other causes of abnormal septal activation. Tracings suggestive of LSFB were encountered in approximately 0.5 % of ECGs reviewed. However, the author argued no example of prominent anterior QRS forces was found in this study which could be clearly differentiated from a normal variant (MacAlpin 2002). The author concluded the left septal block is polymorphic conduction defect, a phenomenon probably explaining some of the previously inadequately understood ECG abnormalities.

Likewise, the clinical significance of a chronic LSFB in a general population remains as a mystery yet to be discovered.

2.9 Incomplete Right Bundle Branch Block

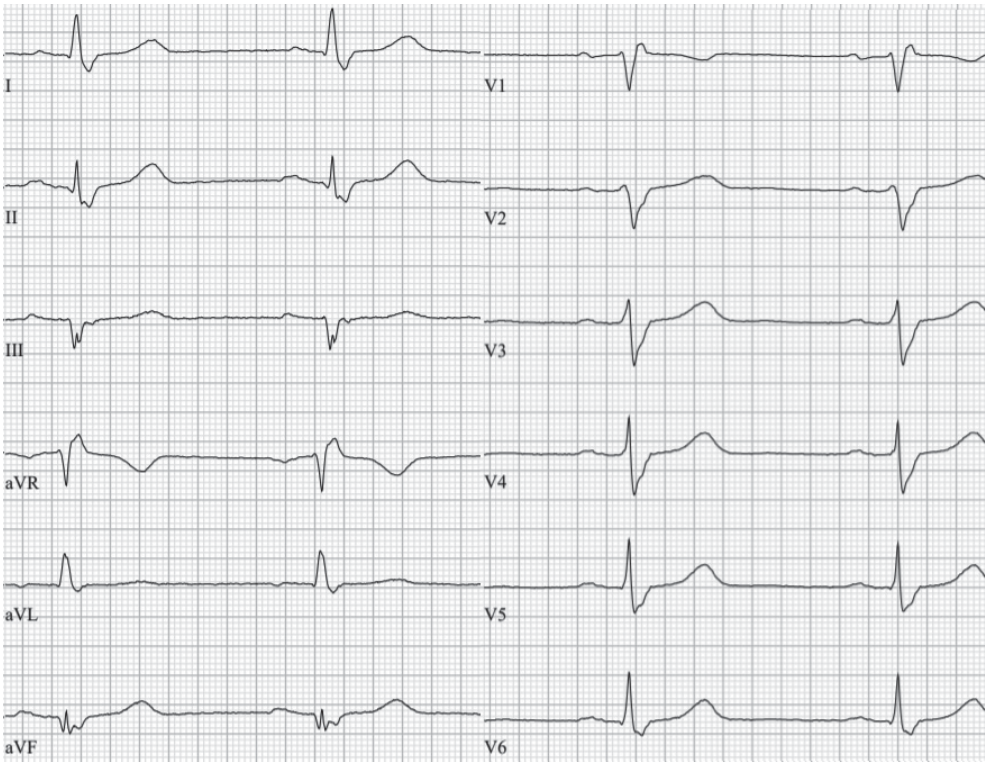
After diverging from the left Hisian system, the right bundle branch proceeds within the right side of the interventricular septum towards the apex of the right ventricle (Davies and Harris 1969), entering the septomarginal trabecula (moderator band) to reach the base of the anterior papillary muscle. At this point, the right main stem divides into numerous strands forming three main subdivisions: anterior, posterior, and lateral. The septomarginal trabecula carries the *lateral* subdivision forming two or more main trucks comprising the largest strands of the right bundle branch to the right ventricular wall and providing the electrical activation for the basal right ventricle. The strands of the *posterior* subdivision pass along from the base of the anterior papillary muscle to the inferior part of the posterior papillary muscles at which point smaller branches are supplied to the posterior right ventricular wall. The *anterior* primary branches proceeded anteriorly on the inferior septal wall, ramifying along the trabeculae carneae of the anterior right ventricular wall (Uhley and Rivkin 1960, 1961, Hishida 1969).

Judgements vary on the nature and meaning of the pattern of iRBBB. Early experimental work on canine (Uhley and Rivkin 1961) and later on humans with "touching" the right bundle with a catheter (Peñaloza et al. 1961) provided evidence of the block as an abnormality in cardiac conduction. Tapping the human right main bundle branch with catheter also resulted in various degrees of RBBB. In minor degrees of RBBB there is slurring of the S wave or a small r' in lead V1 (RSr') with

decreasing voltage of the S wave and prolonged ventricular activation time only of milliseconds. Increasing degrees of the block increase the height of the secondary r' wave, eventually exceeding the primary R wave (rSR'). A third-degree RBBB corresponds to complete RBBB with commonly rsR' pattern but occasionally with rR' pattern or a broad R wave with early notching. This pattern was observed when QRS duration reached 120 ms but interestingly, occasionally even with lesser values (Peñaloza et al. 1961). First- and second-degree RBBBs represent minor types of this conduction delay and are referred as iRBBB.

The location of the block can be proximal (delayed impulse in the right bundle branch trunk) or peripheral. From the ECG viewpoint, a fine-cutting of the large lateral subdivision of the right bundle resulted in a classical iRBBB pattern with prominent R' wave (Uhley and Rivkin 1961, Hishida 1969). Alternatively, it resulted in rather deep S waves in precordial leads with reduced height of the R waves, a pattern often encountered in cor pulmonale and pulmonary emphysema in a clinical practice. On the other hand, rS complex with slurring of the S wave would result from a conduction defect in the right posterior subdivision (Uhley and Rivkin 1961).

Figure 14. Incomplete Right Bundle Branch Block.



In iRBBB the characteristic RSR' morphology (Figure 14) is present in either of the leads V1-V2. The guidelines of the American College of Cardiology and the American Heart Association (Surawicz et al. 2009) and the European Society of Cardiology (Brignole et al. 2018) require a QRS duration between 110 and 119 ms in combination of RSR' pattern for the diagnosis of iRBBB. The Minnesota coding scheme (Prineas et al. 2009) defines iRBBB as R<R' in either of the leads V1-V2. Correspondingly, R≥R' in either of the leads V1-V2 is classified as the R-R' pattern.

In lead V1-V2, the presence of R>R' or R<R' may be due to misplacement of the ECG electrodes in the 2nd or 3rd intercostal place, especially when accompanied by a negative P wave in lead V1. In a previous study, the R-R' pattern disappeared when the electrodes were properly positioned (Baranchuk et al. 2015). Alterations in shape of the chest (pectus excavatum) may also expose the pattern (Wachtel et al. 1956). Other benign conditions include late physiologic activation of the myocardium near the right ventricular outflow tract (Tapia and Proudfit 1960) or as a normal variant due to a delay in the activation of the basal part of the right ventricle (Baranchuk et al. 2015).

For all enlightened clinicians, a new-onset iRBBB may be a harbinger of a potentially life-threating pulmonary embolism due to right ventricular pressure overload (Digby et al. 2015). In a study with dogs (Moore et al. 1971), Moore reported that iRBBB was caused by focal hypertrophy of the right ventricle and not by a delay in the right-sided Hisian conduction system. Congenital heart diseases including septal defects and cyanotic heart defects may also produce the pattern of iRBBB (Tapia and Proudfit 1960).

IRBBB has also been associated with exercise-induced physiological left ventricular remodeling and right ventricular enlargement (Kim et al. 2011) and degenerative heart disease of the elderly (Nielsen et al. 2011). Thus, iRBBB observed in early life may be of a different etiology than in the elderly.

In 1958, Lenègre studied 33 cases of chronic iRBBB. In his histopathologic studies there was almost a complete destruction or significant lesions in the right bundle branch in one quarter of the cases. In three quarters of the cases, the right bundle branch was normal or almost normal. However, there was relative or marked right ventricular hypertrophy in these cases (Lenegre 1958, Lev 1960). These early findings are consistent with the etiology of iRBBB pattern as discussed.

The prevalence of iRBBB in the general population has been around 3 – 5 % with approximately twice the prevalence in men compared to women (Bussink et al. 2013, Haataja et al. 2013). In older Michigan study (n = 5 138) consisting 85 % of the adult population (Ostrander Jr et al. 1965), iRBBB was more frequent among men but no

exact prevalence rate was reported. None of the physiologic abnormalities examined occurred with significant frequency among this group.

IRBBB is a common finding at all ages. The Copenhagen City Heart Study (Bussink et al. 2013) established an U-shaped association with age as iRBBB was more common in individuals aged <30 years and in elderly participants than in middle-aged subjects. In line, in the pre-participation screening of young athletes, iRBBB was one of the most frequent findings with highest proportional prevalence in the youngest (<20 years) group (Pelliccia et al. 2007). The prevalence of iRBBB has been estimated to range from 35 to 50% in athletes, especially in those engaged in endurance sports, compared with less than 10% in young, healthy controls (Corrado et al. 2010). The RBBB morphology has been shown to be reversible with deconditioning (Fagard et al. 1983).

2.9.1 Prognostic Implications

To date, the Copenhagen City Heart Study (n = 18 441) (Bussink et al. 2013) remains one of the largest studies evaluating the prognostic implications of iRBBB in a general population. In this study, iRBBB (n = 624) was not associated with any adverse outcomes including mortality, pacemaker insertion, new-onset heart failure, atrial fibrillation, myocardial infarction, and chronic obstructive pulmonary disease within a median follow-up of 20.5 years. IRBBB at the baseline examination was a significant predictor of a newly acquired complete RBBB during the follow-up though the number of participants later developing a complete RBBB was small and did not allow for subgroup analysis regarding prognosis. Similar results were reported in an older Chicago Western Electric Company Study consisting of 1 960 men (Liao et al. 1986) as those with iRBBB had a greater, though small, likelihood of developing a complete RBBB during a mean 11 years of follow-up. Even in this study, iRBBB was not associated with risk of death from CV diseases in 20 years whether the block was prevalent (n = 134) or incident (n = 222). In a cohort study of the Barcelona city area (n = 2 981), iRBBB (n = 134) was not associated with any adverse CV outcomes in subjects with no history of a CV disease (Alventosa-Zaidin et al. 2019).

In a presumably healthy population of male individuals performing civil flying activities (n = 6 915) (Canaveris 1986), 41 cases of a complete RBBB were noted – in 50 % of them there was a iRBBB pattern before the appearance of a complete RBBB. In the Manitoba Study of pilot men followed for 29 years (n = 3983) (Rabkin

et al. 1981), iRBBB (n = 626) was associated with a small but a significantly increased risk of complete RBBB. The increased risk of a complete RBBB was especially observed in those with iRBBB and a QRS duration 100 ms to 120 ms as compared to those with iRBBB and a QRS duration <100 ms.

In the National Health and Nutrition Examination Survey (n = 6 398), neither R≥R' pattern nor R<R' were associated with mortality in subjects free of a CV disease (O'Neal et al. 2015). Likewise, in a Finnish study of older men (n = 697), R≥R' pattern was not associated with myocardial infarction or all-cause mortality (Tervahauta et al. 1996).

Zhang et al. studied the relation between IVCDs and the risk of mortality in the Atherosclerosis Risk in Communities study cohort (n = 15 408). They found out that while the prevalence of iRBBB (n = 109) and the R-R' pattern (n = 96) appeared rather similar (0.7 % and 0.6 %, respectively), the crude mortality rates were almost double in those with iRBBB as compared to those with the R-R' pattern (Zhang et al. 2016). No adjustments for existing CV risk factors and diseases were provided.

Nielsen et al. reported a novel finding that iRBBB (n = 187) was strongly associated with early-onset lone atrial fibrillation when compared with healthy gender- and age-matched controls (Nielsen et al. 2011). However, data of physical activity was not collected potentially producing some bias to the study results as both iRBBB and atrial fibrillation have been previously associated with endurance sports (Corrado et al. 2010). Association with atrial fibrillation was not seen in two other Danish studies (Bussink et al. 2013, Rasmussen et al. 2019), but interestingly, iRBBB was linked to an increased risk of pacemaker implantation in women (n = 426) but not in men (n = 887) (Rasmussen et al. 2019).

In a study of adults referred for nuclear exercise testing to evaluate known or suspected coronary artery disease (n = 7 073), patients with iRBBB (n = 305) displayed no increased risk of mortality (Hesse et al. 2001).

2.10 Incomplete Left Bundle Branch Block

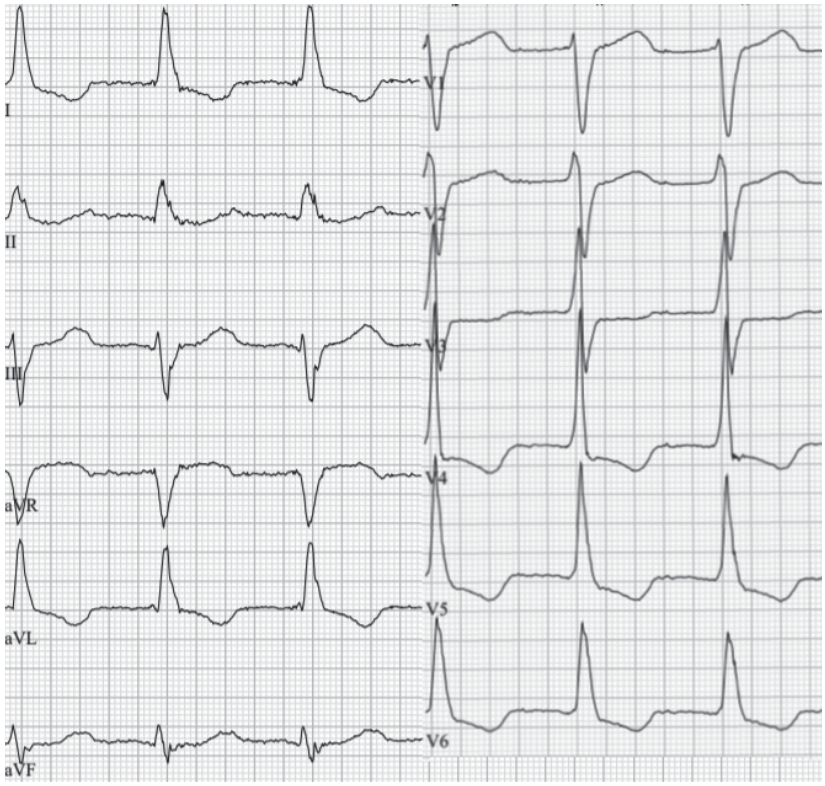
In 1952, Rodriguez published ECG evidence of different degrees of LBBB after cutting a canine left bundle branch (Rodriguez and Sodi-Pallares 1952). Along with increasing QRS duration, slurring of the QRS complex appeared on lead II with minor secondary repolarization changes before turning into a complete LBBB. With slight degrees of block, only a delayed R-peak time and a slight increase in R wave voltage was observed. Similar increase in R wave voltage in minor degrees of LBBB was obtained two years earlier after "touching" a human left main bundle with a catheter (Sodi-Pallares et al. 1950). The authors concluded that the ECG diagnosis of iLBBB is defined by the presence of slurring of the ascending limb of R wave in left lateral leads. Absence of Q waves in same leads also suggest iLBBB, but in cases of iLBBB the QRS duration may be even less than 110 ms as commonly defined.

In the following years, several cases of rate-dependent gradual progression from normal conduction to iLBBB and to complete LBBB were published (Gardberg and Rosen 1958, Schamroth and Bradlow 1964, Barold et al. 1968, Barold and Schamroth 1973). Disappearance of the tiny septal Q waves in left lateral leads was the earliest recognizable sign of iLBBB and increasing degrees of LBBB were manifested by progressive notching or slurring of the ascending R wave leading to increased R-peak time and increased QRS duration and voltage.

In a histopathologic study of four hearts with iLBBB from 1968, the ECG diagnosis correlated with the presence of incomplete lesions in the left bundle branch (Unger et al. 1968). However, all four hearts had also LVH and CHD with jeopardized myocardium. In the work of Lev in 1975 (Lev et al. 1975), in five cases diagnosed as iLBBB there were lesions in the left main bundle such as fibroelastic replacement and fat tissue replacement with no constant finding in the peripheral portion of the left bundle branch. The heart was hypertrophied in all five cases. In the pioneer work of Lenègre in 1958, 37 cases of chronic iLBBB were found. The pattern was almost always associated with significant lesions in the left bundle branch. The most important ECG alterations indicating a severe organic lesion in the fibers of the left bundle branch appeared to be the disappearance of Q wave in left lateral leads and its replacement by a notch in the ascending R wave. The clinical disease was most often hypertensive or ischemic heart disease, or aortic disease. (Lenegre 1958, Lev 1960)

The guidelines of the American College of Cardiology and the American Heart Association (Surawicz et al. 2009) define iLBBB as absence of Q wave in leads I and V5-V6 in the presence of LVH pattern with R-peak time >60 ms in leads V4-V6 with QRS duration between 110 and 119 ms. The Minnesota coding scheme (Prineas et al. 2009) defines iLBBB as QRS duration ≥100 ms but <120 ms in absence of other ventricular blocks or significant Q waves (Figure 15).

Figure 15. Incomplete Left Bundle Branch Block.



It is very likely that lower degrees of LBBB are clinically interpreted as LVH instead of iLBBB. In fact, it has been demonstrated that the ECG signs of LVH are due to, at least in part, slowing of conduction in the left-sided infra-Hisian conduction system (Piccolo et al. 1979). However, by no means there could not be coexisting hypertrophy as well and the hypertrophy could well be the cause of the of the

conduction block. Thus, a significant overlap exists between the ECG diagnosis of LVH and iLBBB.

The prevalence of iLBBB in the general population is not well-established. In the Finnish cohort of males 65 to 84 years old (n = 697) of the Seven Countries study (Tervahauta et al. 1996) the prevalence of iLBBB was 0.7 %. Haataja et al. previously reported (n = 6 299) that the prevalence of iLBBB (n = 69) was 1.0 % and was strongly associated with male sex (Haataja et al. 2013). In a study of French aircrew members examined for fitness assessment (n = 69 186) (Monin et al. 2016) with mean age of 32 and 28 years for males and females respectively, the overall prevalence of iLBBB (n = 21) was only 0.03 % in this extremely healthy population.

2.10.1 Prognostic Implications

The clinical profile and natural history of patients with iLBBB are poorly investigated and remain therefore largely unknown. In the Finnish cohort of ≥ 65-year-old subjects (n = 697) of the Seven Countries study (Tervahauta et al. 1996), 5-year rate of fatal myocardial infarction and mortality were both 20 % for iLBBB (1 of 5 patients). In an another Finnish study (Haataja et al. 2015), iLBBB (n = 69) was not associated with increased risk of CV mortality.

The study of Senesael et al. of a Belgian University Hospital adult in- and outpatients remains as one of the largest studies establishing the characteristics of patients with iLBBB (n = 321) and the first study assessing the progression of an incomplete LBBB to a complete LBBB (Senesael et al. 2020). The median QRS duration was 112 ms at the diagnosis of iLBBB and only 18 % of patients with iLBBB had no overt heart disease. During the median follow-up of 21 months, 33 % of patients with iLBBB progressed to a non-strict LBBB (QRS duration ≥120 ms; traditionally the threshold for a complete LBBB) and 27 % of patients with iLBBB evolved to a 'strict' LBBB defined by the Strauss criteria (Strauss et al. 2011). While those with iLBBB pattern evolving into a complete LBBB were older and more often had reduced left ventricular ejection fraction, no large differences were observed between patients with or without progression to complete LBBB. The findings of this unique study suggest that iLBBB and complete LBBB are entities within the same pathophysiologic spectrum of the conduction delay in the left bundle branch and presumably only differ by the degree of impaired left ventricular conduction.

However, differential diagnosis from LVH with QRS widening is not straightforward, and some investigators consider the ECG diagnosis even somewhat controversial (Haataja et al. 2013). In the Jackson Heart Study (n = 5 146) consisting of African Americans (Mentz et al. 2015), individuals with a mild conduction delay (defined as QRS duration 100 – 119 ms; n = 1 360) had an increased 8-year risk of all-cause mortality even after adjustment for LVH. Furthermore, of 2 599 individuals who had a normal QRS duration at baseline, the QRS duration prolonged in 170 of them (6.5 %) in 6 to 12 years of follow up – the greatest risk was associated with a prior myocardial infarction and LVH. However, in the National Health and Nutrition Examination Survey (n = 8 527) (Badheka et al. 2013), QRS duration 100 – 119 ms was not associated with increased CV mortality after adjusting for confounding factors including LVH, or after excluding those with a prevalent CV disease including LVH.

Zhang et al. reported that individuals with QRS duration ≥100 ms but <120 ms (n = 3 004) had an increased risk of CHD death but not overall mortality in a mean 21 years of follow-up in the Atherosclerosis Risk in Communities study (n = 15 408) (Zhang et al. 2016). This group consisted of patients with LVH (12 %), LAFB (1 %), iRBBB (4 %), the R-R' pattern (3 %), Q waves (14 %), and iLBBB (66 %). Increased risk of new-onset heart failure was also seen in this combined group of patients in another study of the same cohort but this was not true after excluding those with a prevalent CV disease at the baseline (Zhang et al. 2015). Lone iLBBB (defined by the Minnesota definition, n = 1 977) accounted for 41 % of the CHD deaths and 54 % of all-cause mortality of this combined group of ECG findings (Zhang et al. 2016). However, the reported prevalence of iLBBB pattern in this study (12.8 %) was over ten-fold of that which was previously reported in two Finnish studies (Tervahauta et al. 1996, Haataja et al. 2013).

2.11 Left Ventricular Hypertrophy

LVH is defined as an increased left ventricular mass, and it can occur either through ventricular wall thickening or ventricular dilation (Khouri et al. 2010). Epidemiological studies have shown that increasing age, obesity (Lauer et al. 1991), and elevated blood pressure (Kannel 1983) are risk factors for the development of LVH. At the population level, the most important risk factor for LVH is hypertension (Kannel 1992). Other causes for sustained pressure induced LVH include aortic stenosis, while aortic and mitral regurgitation account for many cases of LVH induced by volume overload. LVH may also be a manifestation of several different diseases affecting structural and functional proteins of cardiomyocytes as cardiomyopathies (most commonly hypertrophic, or dilated cardiomyopathy), or rarely, a cardiac manifestation of a storage or a metabolic disorder (amyloidosis, Fabry disease) (Linhart and Cecchi 2018). LVH can also be a physiologic adaptation to high-intensive physical training (athlete's heart) with no pathologic changes in cardiac systolic or diastolic function (Pluim et al. 2000).

The leading component in pathological LVH is increased myocardial fibrosis. Increased myocardial fibrosis is a common endpoint of many cellular and non-cellular pathologic processes in hypertensive heart disease is and it has been linked to the development of LVH (Janardhanan and Kramer 2011).

LVH has been causally related to high blood pressure, and its presence in a hypertensive patient has been established as hypertensive target organ damage (Levy et al. 1994). LVH is a strong independent predictor of future CV events and a risk factor for CHD, heart failure, arrhythmias, stroke, and for mortality including sudden cardiac death (Artham et al. 2009, Bang et al. 2017). The presence of ECG-LVH was associated with an increased risk of congestive heart failure even after adjustment for CHD (Levy et al. 1996). In fact, the data from the Framingham Heart Study indicated LVH was more potent risk factor for heart failure than it was for CHD events (Kannel 1983). The Atherosclerosis Risk in Communities study showed that in middle-aged individuals with ECG-LVH, the most common first CV event was CHD or non-fatal myocardial infarction in men, while heart failure was more likely to be the first CV event in women (Desai et al. 2012).

The classic strain pattern of ST depression and T wave inversion on ECG is a well-established marker of the presence of anatomic LVH (Okin et al. 2001), and ECG-LVH associated with repolarization abnormalities is, unfortunately, an ominous harbinger of CV events (Kannel et al. 1972, Okin et al. 2004b). In the Framingham Heart study, half of those who developed LVH with strain pattern had

LVH but without repolarization abnormalities present on their prior ECG. Originally, voltage-only LVH was described carrying half the prognostic information of ECG-LVH with repolarization abnormalities in respect to future CHD events, and after adjustment for blood pressure levels the excess risk was virtually obliterated (Kannel et al. 1970). However, in the Copenhagen City Heart Study, voltage-only LVH (defined by Minnesota code) was associated with fatal and non-fatal ischemic heart disease events in subjects over 55 years old during 21 years follow-up (Larsen et al. 2002), in contrast to Framingham study findings.

The original criteria for ECG-LVH were developed in reference to autopsy studies (Lewis 1914) or clinical data of patients in whom a cardiac disease was capable of producing increased strain of the left ventricle (Sokolow and Lyon 1949). Generally, ECG has a low sensitivity but a high specificity for detection of anatomic LVH (Hancock et al. 2009). Nowadays, the cardiac magnetic resonance imaging has been established as a golden standard for the estimation of left ventricular geometry and detection of LVH (Janardhanan and Kramer 2011). In the Multi-Ethnic Study of Atherosclerosis cohort, the specificity of each ECG-LVH criteria in reference to LVH defined by cardiac magnetic resonance imaging was 92.6%, 95.5%, and 97.3% for Sokolow-Lyon voltage, Minnesota criteria, and Cornell voltage, respectively. The sensitivity of each criteria was poor (under 30 % at the best) (Jain et al. 2010). The performance of each ECG-LVH criteria also seem to vary substantially by ethnicity (Jain et al. 2010), obesity (Okin et al. 2000), while increased blood pressure and smoking were related to a false-negative ECG-LVH (Bacharova et al. 2015).

Diastolic dysfunction is one of the earliest manifestations of a hypertensive heart disease, and it has been correlated with the development of LVH. In early hypertension, there is an evidence of decreased diastolic distensibility and delayed relaxation of the left ventricle (Janardhanan and Kramer 2011). Diastolic filling abnormalities have been associated with the development of congestive heart failure (Aurigemma et al. 2001), and LVH is the most common myocardial structural abnormality associated with heart failure with preserved ejection fraction (Heinzel et al. 2015). In a severe hypertensive heart disease, left ventricle can develop systolic dysfunction as well. In a retrospective study of patients with concentric LVH and normal ejection fraction on prior echocardiogram, systolic pump dysfunction occurred in 13 % of the patients after a mean follow-up of 33 months (Milani et al. 2011). This deterioration of ventricular function was most commonly associated with a development of myocardial infarction within the follow-up (in 43 % of the patients). Interestingly, a QRS duration ≥120 ms (in combination of echocardiographic LVH) was also associated with left ventricular systolic

dysfunction in this study. In the Losartan Intervention For Endpoint Reduction in Hypertension study, increased QRS duration in combination of ECG-LVH was related to increased risk of future CV events in the setting of aggressive hypertensive therapy (Oikarinen et al. 2004), but population-wide studies of the subject are lacking.

3 AIMS OF THE STUDY

The aim of this study was to provide contemporary knowledge regarding the prognostic significance of intraventricular conduction delays in the standard 12-lead resting ECG in a general adult population. We were especially interested in the risk of mortality and heart failure associated with these electrocardiographic findings.

The specific aims of this present study were:

1. To elucidate the long-term prognostic implications of intraventricular conduction delays on cardiovascular morbidity and mortality (I)

2. To evaluate the impact of the definition of left bundle branch block on long-term outcome in the general population (I)

3. To study the relation of intraventricular conduction delays to a risk of new-onset heart failure and structural heart disease (II)

4. To characterize the prevalence and baseline cardiovascular risk factors in relation to QRS duration in left ventricular hypertrophy (III)

5. To investigate the long-term prognostic implications of QRS duration in left ventricular hypertrophy (III)

4 MATERIALS AND METHODS

This study was conducted as a part of the Health 2000 survey, which consists of a random sample of a predominantly Caucasian general population with applicable phenotype data collected at the baseline and with over 15 years (median 15.9 years) of follow-up data.

4.1 Study Population

A representative stratified random sample of the Finnish population was examined in the Health 2000 Survey. The Survey was carried out in 2000–2001 by comprehensive methods. The purpose of the Survey was to provide up-to-date epidemiological data of major public health problems in Finland, their causes and treatment. Special emphasis was placed on CV diseases. The study material is of high quality, and it represents the whole population unusually well. The sampling included both the largest cities and smaller regions and suburbs. In addition to the household population, people living in institutions were included. Geographically, the autonomous territory of Åland Islands was excluded, as were people living on islands not accessible by road. The Health 2000 involved two separate surveys: the main survey was carried out in the population aged 30 years or over, and the study of young adults focused on people aged 18–29. In order to obtain a sufficient number of observations from the oldest age cohorts in the main survey, the sampling probability was twice as high for the population aged ≥80 years as among those under 80 years. The implementation of the Survey has been described in depth previously (Heistaro 2008).

The main Health 2000 sample comprised 8 028 individuals (3 637 men and 4 391 women) aged 30 or older. The final sample of the main Survey comprised 7 979 individuals as 49 subjects deceased before the field work. Of the final main Survey sample, 79 % (6 354 individuals; 2 876 men and 3 478 women) participated in the health examination.

4.1.1 Collection of Clinical Phenotype Data

After a home interview, a comprehensive health examination including questionnaires, measurements, a resting 12-lead ECG, and physician's physical examination was performed. The health examination was performed on each participant 1–6 weeks later at a local health center by centrally trained professional doctors and nurses. The National Care Register for Health Care and the National Register on Rights to Reimbursements for Medication costs were linked to the Health 2000 Survey data.

Standard 12-lead ECGs were recorded in the resting supine position by MAC 5000 recorders (Marquette Hellige, Freiburg, Germany and Milwaukee, WI, USA) and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige, Milwaukee, WI).

Among 6,354 subjects attending the health examination, there were 36 for whom an ECG was not possible to obtain. The reasons for not succeeding were recorded by the investigators with entries such as "difficult to move," "wheelchair", "denial", "leg/hand amputated", "in geriatric chair", "massive hernia" and "plaster in leg/hand".

ECG was obtained successfully in 6 318 individuals (99 % of the individuals attending the health examination). All ECGs were read, and the computerized diagnoses and measurements corrected if needed, by a physician experienced with ECG before being stored in the database. The ECGs were recorded and printed using a paper speed of 50 mm/s. The maximal filter setting of the system (150 hertz) was used.

In the further process, 19 ECGs were lost (diskette lost 9, coupling error 4, data reading failure 5, unspecific reason 1), leaving 6 299 ECG recordings for the study. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding scheme (Prineas et al. 2009). Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators who were blinded to the clinical data of the patient. The electrical recordings were analyzed by means of Magellan software program (Marquette Electronics Inc., Milwaukee, WI, USA).

The health examination included measurements of height, weight, body mass index (BMI), and blood pressure. Height was recorded to an accuracy of 0.5 cm. Weight (in underpants) was measured to the nearest 0.1 kg.

Blood pressure was measured after the subjects had been seated quietly in the measurement room for at least five minutes. It was always measured with a mercury

sphygmomanometer (Mercuro 300, Speidel & Keller, Juningen, Germany) from the right arm, if possible. The width of the rubber cuff was 12 cm and its length 35 cm. If the proximal circumference of the upper arm measured at a height of 5 cm from the crook of the arm was in excess of 35 cm, a larger cuff (width 15, length 43 cm) was used. Systolic pressure was recorded at the appearance of the first Korotkoff sounds to an accuracy of 2 mmHg. Diastolic pressure was also recorded to an accuracy of 2 mmHg at the fifth phase of the Korotkoff sounds, when the latter of two consecutive sounds was no longer audible. A second set of readings was taken two minutes after the first measurement. The average of the two measurements was used in the analysis. The quality of blood pressure and heart rate measurements was constantly monitored during the field examinations and in connection with separate quality control checks during which measurements were taken from people who were not included in the study population (Anttila 2014). Hypertension was defined as a clinic average blood pressure ≥140/90 mmHg or right to drug reimbursements for hypertension.

Venous blood samples were drawn from the antecubital vein. Laboratory tests included measurements for high-density lipoprotein cholesterol (HDL), total cholesterol, triglyceride, serum glucose, serum uric acid concentration, high-sensitivity c-reactive protein concentration, and gamma-glutamyltransferase activity concentration. Low-density lipoprotein cholesterol (LDL) was calculated with the Friedewald formula.

Diabetes mellitus was defined as a serum glucose level of 7.0 mmol/L or greater or a history of the use of oral hypoglycemic agents or insulin therapy. Heart murmur was defined as a systolic or diastolic murmur heard at physician's physical examination. Smoking was defined as daily use of tobacco products.

Classification of CHD required at least one of the following: diagnosis of myocardial infarction and/or angina pectoris during the field health examination by a physician, pathological Q waves in the resting ECG indicating a previous myocardial infarction, a previous diagnosis of CHD (International Classification of Diseases [ICD]-8 or ICD-9 codes 410–414 or ICD-10 codes I20–I25) from the Care Register for Health Care, a history of coronary revascularization procedure, the right to drug reimbursements for CHD, or the use of nitroglycerine combined with an anticoagulant, acetyl salicylic acid, or beta-blocker.

Classification for myocardial infarction required either a clinical diagnosis of old myocardial infarction by the examining physician, pathological Q waves in the resting ECG indicating a previous myocardial infarction, or a previous diagnosis of myocardial infarction from the Care Register for Health Care (ICD-8 or ICD-9 code

410 or ICD-10 codes I21–I22). Old myocardial infarction was defined as a positive history of the condition in the medical records or old myocardial infarction on ECG, or typical self-reported history of myocardial infarction treated in a hospital. Q waves indicating probable previous myocardial infarction included Minnesota codes 1.1–1.3. The Finnish Care Register for Health Care has been shown to be valid in identifying major CHD events (Pajunen et al. 2005).

Heart failure classification required a clinical diagnosis by the examining physician or a previous diagnosis of heart failure (ICD-8 code 4270, ICD-9 code 428, or ICD-10 codes I11.0; I13.0; I13.2; or I50) from the Care Register for Health Care, or the right to drug reimbursements for heart failure. The Finnish Care Register for Health Care has been shown to be valid in identifying heart failure diagnoses and can be reliably used for research purposes (Vuori et al. 2019).

The classification for structural heart disease required a previous diagnosis of structural heart disease (ICD-9 codes 39, 425, 746, or ICD-10 codes I34–I37, I39, or I42).

The classification for stroke required one or more discharge diagnoses of stroke (ICD-8 codes 430–431, 433–434, ICD-9 codes 430–434, or ICD-10 codes I60, I61, I63). Classification for peripheral arterial disease required a clinical diagnosis by the examining physician or previous hospitalization for peripheral arterial disease.

4.1.2 Data Protection and Ethical Approval

A major consideration at all stages of the Health 2000 Survey was the provision of data protection and the appropriate handling and storage of all data and materials collected. Every possible precaution was taken to prevent unauthorized access. In the examination files, personal data were replaced by examination codes; even the researchers analysing the final data no longer have access to any personal data. However, since these data will be needed for follow-up purposes as well as for linking with other data, they are accessible to a small number of authorized personnel for these specific purposes (Anttila 2014). The study protocol of the Health 2000 survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. An information letter was handed out to the subjects in connection with the home interviews by Statistics Finland staff and later in connection with the health examinations. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

4.2 Main Exposure Variables

The main exposure variables were IVCDs and/or QRS duration in all three studies. For their identification, both Minnesota codes and measurements based on the Magellan software program were used. Six of the conduction delays were classified according to the respective Minnesota classes: $LBBB_{MC}$ (code 7-1), RBBB (code 7-2), iRBBB (code 7-3), non-specific $IVCD_{MC}$ (code 7-4), the R-R' pattern in either of leads V1, V2 with R' amplitude ≤R (R-R') (code 7-5), and iLBBB (code 7-6). For LAFB we used the following definition: frontal QRS axis between –30° and –90°, rS configuration in II, III, and aVF, and qR configuration in aVL, with a QRS duration less than 120 ms. LPFB was defined as frontal QRS axis >120°, lead I rS configuration, leads II, III, and aVF qR configuration, and no pathological Q waves in leads II, III, aVF.

In study I, two different definitions for LBBB and non-specific IVCD were used: conventional (Minnesota: $LBBB_{MC}$) and the Strauss definition ($LBBB_{STRAUSS}$) (Strauss et al. 2011). The Strauss definition of LBBB include a QRS duration ≥140 ms for men and ≥130 ms for women, along with mid-QRS notching or slurring in ≥2 contiguous leads. Non-specific $IVCD_{STRAUSS}$ was defined as a wide ≥120 ms QRS duration without meeting the criteria of RBBB, LBBB by the Strauss definition, ventricular pacing, or Wolff-Parkinson-White pattern. The accuracy of the classification was checked by manual ECG analysis by three of the investigators (JR, PH, and KN). The classifications proved to be accurate.

In studies II and III, LBBB was identified by the Strauss definition. ECGs with a wide ≥120 ms QRS duration without meeting the criteria of RBBB, LBBB by the Strauss definition, ventricular pacing, or Wolff-Parkinson-White pattern were defined as non-specific IVCD.

In study III, the main exposure variable was QRS duration in ECG-LVH. ECG-LVH was identified either by Cornell ($S_{V3} + R_{aVL} > 2.0$ mV for women, >2.8 mV for men; Casale et al. 1985) and/or Minnesota (code 3-1: R_{V5} or R_{V6} >2.6 mV, or R_I or R_{II} or R_{III} or R_{aVF} >2.0 mV, or R_{aVL} >1.2 mV; and code 3-3 which also includes the Sokolow-Lyon criteria: R_I >1.5 mV but ≤2.0 mV, or $R_{V5} + S_{V1}$ >3.5 mV, or $R_{V6} + S_{V1}$ >3.5 mV; Prineas et al. 2009) voltage criteria. ECG-LVH was considered positive if any of the criteria was met.

4.3 Study End Points and Follow-up Data

From the baseline examination between 2000 and 2001, the participants were followed up for the main study endpoints until the end of 2015 (median follow-up time 15.9 years). The follow-up information was gathered by linking the personal identity code from the Health 2000 Survey database to the Care Register for Health Care and the Causes of Death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens in Finland and nearly 100 % abroad. Diagnoses are registered in these registers by the treating physicians with codes defined in ICD-10. The follow-up information was available for all subjects.

In study I, the main prognostic outcomes were CV mortality and all-cause mortality. In additional analyses, the endpoints were a diagnosis of any cardiac disease (including CHD, myocardial infarction, heart failure, atrial fibrillation [ICD-10 code I48 from the Care Register for Health Care or right to drug reimbursements for atrial fibrillation], and structural heart disease) and any CV disease (including any cardiac disease, stroke, peripheral artery disease, diabetes, and hypertension) before the baseline examination throughout the entire period of observation until the end of follow-up.

In study II, two study endpoints were used: new-onset heart failure and structural heart disease. New-onset heart failure was defined as a diagnosis of heart failure with the pre-described ICD-codes for heart failure from the Care Register for Health Care, new right to drug reimbursements for heart failure, or pre-described ICD-codes for heart failure from the Causes of Death Register. New-onset structural heart disease required a diagnosis of structural heart disease with the pre-described ICD-codes for structural heart disease from the Care Register for Health Care, or pre-described ICD-codes for structural heart from the Causes of Death Register. The coding of endpoints was based on the fine work of A. S. Havulinna, V. Salomaa and others at the Finnish Institute for Health and Welfare.

In study III, main prognostic outcomes were CV mortality, all-cause mortality, and new-onset heart failure.

4.4 Study Exclusion Criteria

In study I, there was no exclusion of subjects. The final analysis was performed with 6 299 subjects: 3 442 women and 2 857 men (mean age 52.8, SD 14.9 years).

In study II, to study the incidence of new-onset heart failure and structural heart disease, we excluded subjects with prevalent heart failure or structural heart disease at the baseline health examination. Thus, the analysis was performed with 6 080 subjects: 3 298 women and 2 782 men (mean age 52.1, SD 14.5 years). Additional sensitivity analyses were performed excluding subjects with history of heart disease (CHD, previous myocardial infarction, including Q waves in the resting ECG) and subjects with heart murmurs.

In study III, we excluded subjects with left or right bundle branch block (n = 122), LAFB (n = 69), iRBBB (n = 61), paced rhythm (n = 13) and Wolff-Parkinson-White pattern (n = 1). After these exclusions, the study population consisted of 6 033 subjects: 3 320 women and 2 713 men (mean age 52.2, SD 14.6 years). Participants with a prior diagnosis of heart failure or CHD were further excluded from the analysis when studying QRS duration in ECG-LVH as an independent risk factor for new-onset heart failure in this study.

4.5 Statistical Analyses

In study I, the prevalence of IVCDs was established in six age groups: 30-44, 45-54, 55-64, 65-74, 75-84, and 85 or older. Proportions were compared with the chi-square test or Fisher's exact test. The complex sampling design was taken into account by correcting for the oversampling of subjects over 80 years of age. Data were categorized into eleven groups (study I) according to the presence and type of IVCD (eight IVCDs with two definitions for LBBB and non-specific IVCD), and into nine groups (study II) according to the presence and type of IVCD.

Survival to each endpoint was assessed using the Kaplan–Meier method. Age and sex adjustments were included. Hazard ratios were calculated by univariate and multivariable Cox regression model analysis. Multivariable analysis included the following parameters: age, sex, hypertension, diabetes mellitus, smoking, BMI, LDL cholesterol, CHD, myocardial infarction (studies I, II and III), and heart failure (studies I and III). Death from non-CV causes was considered as a competing event to CV death (studies I and III). To take into account this competing risk, a model according to the method of Fine and Gray subhazards model was applied. This

model did not modify the results of Cox proportional hazard analysis in either of the studies. In study I, we also tested for interaction between intraventricular blocks and CHD or heart failure associating with the risk of mortality by introducing their product as an interaction term.

In study III, the distribution of QRS duration in the study population was visualized by a density plot. The linearity of the association of QRS duration and mortality was checked in a spline model in subjects with ECG-LVH. This showed a clear deviation from linearity with the risk of death increasing clearly above QRS duration of 100 ms. In order to demonstrate the results in clinical context, the population was divided in three subgroups with different QRS durations: <100 ms, 100–109 ms and ≥110 ms. Prognostic implications of QRS duration were studied across these ECG-LVH groups and also further comparing the results to subjects with normal ECG (no LVH and QRS <100 ms). We also tested for interaction between the QRS duration and sex by introducing their product as an interaction term. Interaction for QRS duration and prevalent CHD was also tested similarly. Interaction analyses showed no interaction between QRS duration and sex associating with the risk of mortality or new-onset heart failure, or between QRS duration and CHD associating with the risk of mortality among subjects with LVH ($P > 0.1$ for both).

5 RESULTS

5.1 Prognostic Implications of Intraventricular Conduction Delays on Cardiovascular Mortality and Morbidity (Study I)

The prevalence of IVCDs in the representative Finnish population is illustrated on Figure 16 (based on Table 2). In general, the prevalence of LAFB and blocks with a wide QRS ≥120 ms clearly increased with age. For other conduction delays, there was no clear age-association. In subjects over 85 years of age the overall prevalence of any intraventricular block was 23.4 %. In this elderly cohort, the most common intraventricular block was RBBB with the prevalence of 7.4 % in the population.

Twelve subjects (0.2 % of the whole study population; 16 % of all RBBBs) had a bifascicular block pattern with RBBB. Only one of these had RBBB and LPFB, while eleven had RBBB with LAFB.

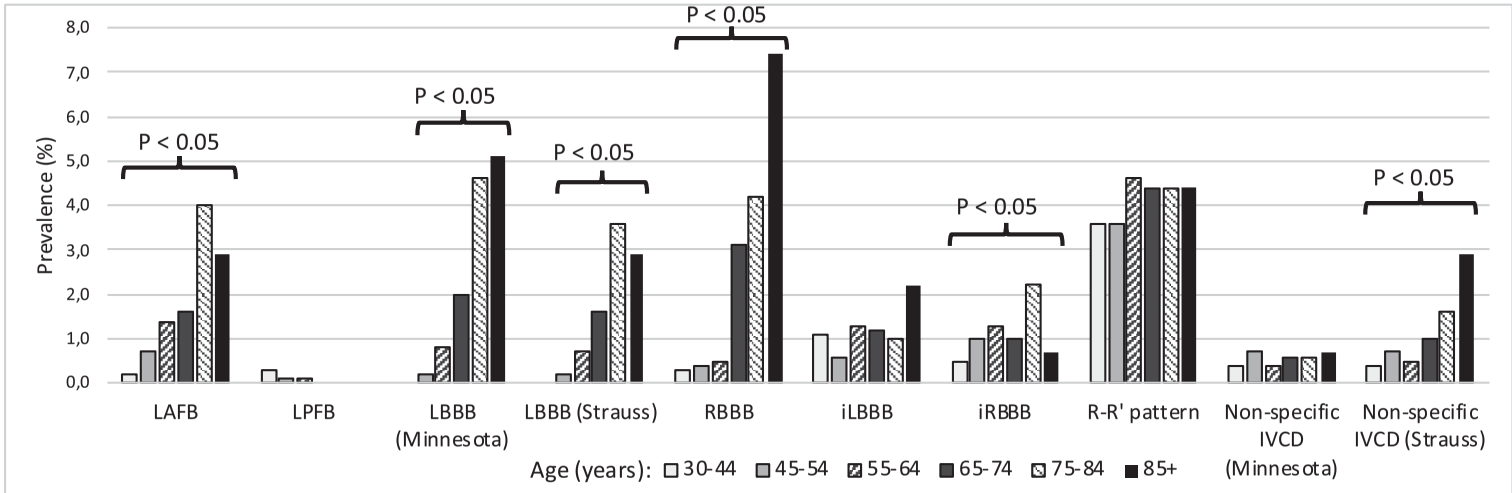
$LBBB_{STRAUSS}$ criteria were met in 80% of subjects positive for the conventional (Minnesota) definition of LBBB.

Table 2. Prevalence of Intraventricular Conduction Delays in Age Groups (Study I).

Intraventricular Conduction Delay	Total n =6299			30-44 =2142	45-54 =1615	55-64 =1088	65-74 =785	75-84 =481	85+ =129
	n	%	95% CI	%	%	%	%	%	%
LAFB	69	1.1	0.9-1.4	0.2	0.7	1.4	1.6	4.0	2.9*
LPFB	8	0.1	0.1-0.3	0.3	0.1	0.1	0.0	0.0	0.0
$LBBB_{MC}$	59	0.9	0.7-1.2	0.0	0.2	0.8	2.0	4.6	5.1*
$LBBB_{STRAUSS}$	47	0.7	0.6-1.0	0.0	0.2	0.7	1.6	3.6	2.9*
RBBB	75	1.2	1.0-1.5	0.3	0.4	0.5	3.1	4.2	7.4*
iLBBB	66	1.0	0.8-1.3	1.1	0.6	1.3	1.2	1.0	2.2
iRBBB	61	1.0	0.8-1.2	0.5	1.0	1.3	1.0	2.2	0.7*
R-R' pattern	249	4.0	3.5-4.5	3.6	3.6	4.6	4.4	4.4	4.4
Non-specific $IVCD_{MC}$	33	0.5	0.4-0.7	0.4	0.7	0.4	0.6	0.6	0.7
Non-specific $IVCD_{STRAUSS}$	45	0.7	0.5-1.0	0.4	0.7	0.5	1.0	1.6	2.9*

CI = confidence interval; MC = Minnesota definition; *P <0.05 for difference between age groups.

Figure 16. Prevalence of Intraventricular Conduction Delays in the Health 2000 Survey (Study I).



LAFB = Left Anterior Fascicular Block; LPFB = Left Posterior Fascicular Block; LBBB (Minnesota) = LBBB by the Minnesota definition; LBBB (Strauss) = LBBB by the Strauss definition; RBBB = Right Bundle Branch Block; iLBBB = Incomplete Left Bundle Branch Block; iRBBB = Incomplete Right Bundle Branch Block (R<R' in V1-V2); R-R' pattern = The R-R' pattern in either of the leads V1-V2 with R≥R'. Non-specific IVCD (Minnesota) = Minnesota definition of non-specific IVCD; Non-specific IVCD (Strauss) = Non-specific IVCD after LBBB was defined by the Strauss definition.

From the original work of J. Rankinen et al. (Rankinen et al. 2021).

Intraventricular blocks proved to carry a high burden of CV diseases and their risk factors. The clinical characteristics of the entire study population stratified by the presence and type of IVCD is presented in Table 3 for continuous variables and Table 4 for dichotomous variables. Briefly, subjects with LBBB, non-specific IVCD, LAFB, and complete or incomplete RBBB were generally older, while RBBB, iLBBB and non-specific IVCD were associated with male sex.

A high prevalence of CV diseases was noted in subjects with LAFB, non-specific IVCD, LBBB and RBBB, while the R-R' pattern, iRBBB and LPFB had no clear relationship with CV diseases. The other blocks showed varied associations with risk factors and studied disease. Heart failure was strongly associated with left and right bundle branch blocks, LAFB and non-specific IVCD, while complete and incomplete LBBB, LAFB, non-specific IVCD, and RBBB were associated with different manifestations of atherosclerosis. Approximately half of the subjects with LBBB had a prevalent CHD regardless of the definition of the conduction delay, while one third of those with RBBB and non-specific IVCD were associated with CHD. Seven out of twelve subjects (58.3 %) with bifascicular RBBB had a diagnosis of heart failure.

Within 10 years of the baseline health examination, 47 % of those with LBBB, 40 % of those with non-specific IVCD, and 37 % of those with RBBB had died. Throughout the entire 15-year period of observation (median 15.9 years), 1 309 of the 6 299 subjects (20.8 %) died and of these 655 (50.0 % of all deaths) were CV deaths. Mortality rates for the intraventricular blocks are presented in Table 4. For overall mortality, subjects with complete and incomplete RBBB, LBBB, LAFB and non-specific IVCD had the highest mortality rates, while for CV deaths the highest rates were found in participants with LBBB, RBBB, non-specific IVCD, and LAFB. More specifically, 80 % of those with non-specific IVCD, and 74 % of those with LBBB and RBBB who deceased, died of CV causes.

Throughout the entire period of observation, only 9 % (n = 4) of individuals with LBBB, 35 % (n = 26) of those with RBBB, and 42 % (n = 19) of those with non-specific IVCD remained free of any known cardiac disease including CHD, heart failure, structural heart disease and atrial fibrillation ($P < 0.001$ for difference between groups). For any CV diseases, only 9 % of individuals with LBBB (n = 4), 20 % (n = 15) of those with RBBB, and 24 % (n = 11) of those with non-specific IVCD remained free of any CV disease ($P = 0.114$ for difference between groups).

Table 3. Baseline Characteristics of Intraventricular Conduction Delays for continuous variables in the Health 2000 Survey (Study I).

	Intraventricular Conduction Delay																					
	No IVCD		LAFB		LPFB		$LBBB_{MC}$		$LBBB_{STRAUSS}$		RBBB		iLBBB		iRBBB		R-R' pattern		Non-specific $IVCD_{MC}$		Non-specific $IVCD_{STRAUSS}$	
Variable	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD	Mean / %	SD
Male (%)	56.6		52.9		75.0		42.4		61.7		62.7*		75.4*		55.7		49.0		90.9*		82.2*	
Age (years)	52.1	14.6	65.4*	14.2	38.8*	12.2	73.2*	10.9	72.0*	11.2	69.8*	14.2	54.2	16.9	58.4*	14.6	54.0	15.2	54.6	15.7	60.7*	17.5
BMI (kg/m^2)	27.0	4.7	26.7	4.6	23.1*	1.6	27.4	4.1	27.3	4.2	27.1	3.9	28.9*	3.8	26.0	4.1	26.0*	4.5	27.8	4.9	27.8	4.7
Total cholesterol (mmol/L)	5.9	1.2	6.3*	1.4	5.6	1.2	6.0	1.2	6.1	1.3	5.9	1.2	5.9	1.0	5.9	1.2	6.1*	1.2	5.8	0.8	5.8	0.8
HDL (mmol/L)	1.3	0.4	1.3*	0.4	1.4	0.4	1.2*	0.4	1.3	0.4	1.3	0.4	1.2*	0.4	1.3	0.4	1.4*	0.4	1.3	0.3	1.2*	0.3
LDL (mmol/l)	3.7	1.0	4.1*	1.4	3.6	1.0	3.7	1.2	3.8	1.2	3.7	1.0	3.8	1.0	3.8	1.2	3.8	1.1	3.7	0.8	3.6	0.8
Triglycerides (mmol/L)	1.6	1.1	1.9*	1.1	1.0	0.3	1.8	1.1	1.7	0.8	1.7	1.1	1.7*	0.8	1.5	0.6	1.6	1.3	1.7	0.9	1.8	1.2

BMI = body mass index; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MC = Minnesota definition; SD = Standard Deviation; *P <0.05 for difference compared to "no IVCD" category.

Table 4. Clinical Characteristics of Intraventricular Conduction Delays (Study I).

	No IVCD n (%)	LAFB n (%)	LPFB n (%)	$LBBB_{MC}$ n (%)	$LBBB_{STRAUSS}$ n (%)	RBBB n (%)	iLBBB n (%)	iRBBB n (%)	R-R' pattern n (%)	Non-specific $IVCD_{MC}$ n (%)	Non-specific $IVCD_{STRAUSS}$ n (%)
Current Smoking	1549 (27.2)	10 (14.7)*	1 (12.5)	9 (15.3)*	8 (17.0)	15 (20.0)	18 (29.5)	12 (19.7)	71 (28.5)	6 (18.2)	7 (15.6)
Hypertension	2671 (46.9)	50 (73.5)*	1 (12.5)	47 (79.7)*	37 (78.7)*	50 (66.7)*	35 (57.4)	31 (50.8)	115 (46.2)	22 (66.7)*	32 (71.1)*
Diabetes mellitus	324 (5.7)	6 (8.8)	0	10 (16.9)*	8 (17.0)*	9 (12.0)*	4 (6.6)	6 (9.8)	7 (2.8)*	2 (6.1)	4 (8.9)
Stroke	213 (3.7)	6 (8.8)*	0	8 (13.6)*	4 (8.5)	6 (8.0)	1 (1.6)	1 (1.6)	14 (5.6)	5 (15.2)*	9 (20.0)*
Peripheral artery disease	82 (1.4)	2 (2.9)	0	6 (10.2)*	4 (8.5)*	3 (4.0)	1 (1.6)	5 (8.2)	4 (1.6)	3 (9.1)*	5 (11.1)*
Coronary heart disease	529 (9.3)	14 (20.6)*	0	31 (52.5)*	24 (51.1)*	25 (33.3)*	8 (13.1)	10 (16.4)	20 (8.0)	10 (30.3)*	17 (37.8)*
Myocardial infarction	189 (3.3)	4 (5.9)*	0	17 (28.8)*	11 (23.4)*	6 (8.0)*	5 (8.2)*	3 (4.9)	10 (4.0)	9 (27.3)*	15 (33.3)*
Heart failure	118 (2.1)	9 (13.2)*	0	12 (20.3)*	9 (19.1)*	13 (17.3)*	3 (4.9)	1 (1.6)*	5 (2.0)	3 (9.1)*	6 (13.3)*
Death											
All-cause	1097 (19.3)	31 (45.6)*	1 (12.5)	37 (62.7)*	27 (57.4)*	45 (60.0)*	14 (23.0)	21 (34.4)*	53 (21.3)	10 (30.3)	20 (44.4)*
Cardiovascular	517 (9.1)	17 (24.6)*	1 (12.5)	27 (45.8)*	20 (42.6)*	33 (44.0)*	10 (15.2)	9 (14.8)	31 (12.4)	9 (27.3)*	16 (35.6)*

MC = Minnesota definition; SD = Standard Deviation; *P <0.05 compared to No IVCD category

In the age- and sex-adjusted Cox regression analysis (Table 5), the hazard ratio for CV death for $LBBB_{MC}$ was 2.05 (95% confidence interval [CI] 1.39–3.02, P < 0.001), for $LBBB_{STRAUSS}$ 1.77 (95% CI 1.13–2.77, P = 0.012), for non-specific $IVCD_{MC}$ 2.76 (95% CI 1.43–5.35, P = 0.003), and for non-specific $IVCD_{STRAUSS}$ 3.15 (95% CI 1.91–5.18, P < 0.001). After controlling for known clinical risk factors, LBBB defined by conventional criteria ($LBBB_{MC}$) and non-specific IVCD regardless of the definition retained their statistical significance to predict CV death.

$LBBB_{MC}$, but not $LBBB_{STRAUSS}$, was associated with higher overall mortality in age- and sex-adjusted Cox regression analysis (95% CI 1.49, 1.07–2.07, P = 0.018), but not after controlling for clinical risk factors. Subjects with non-specific IVCD were associated with higher overall mortality both in age- and sex-adjusted (95% CI 2.07, 1.33–3.23, P = 0.001) and multivariable-adjusted (95% CI 2.01, 1.27–3.18, P = 0.003) Cox regression analysis after LBBB was defined with the Strauss

definition. This excess risk of all-cause mortality was driven by a strong association with CV mortality. Non-specific $IVCD_{MC}$ was associated with over 50 % increased risk for all-cause mortality, but the result was not statistically significant.

RBBB was not associated with higher CV or all-cause death after adjustment for age and sex and after multivariable adjustment for CV risk factors and diseases. In contrast, bifascicular RBBB was associated with higher rate of CV mortality (95% CI 2.70, 1.20–6.05, P = 0.016) after adjustment for age and sex. After controlling for known clinical risk factors, the hazard ratio for CV mortality for bifascicular RBBB was 1.53 (95% CI 0.67–3.52, P = 0.313).

Incomplete bundle branch blocks and lone fascicular blocks were not associated with increased mortality rates after controlling for clinical risk factors in the Cox regression analysis.

Table 5. Adjusted Cox Proportional Hazard Analysis for Cardiovascular Mortality (Study I).

Intra-ventricular Conduction Delay	Unadjusted			Age- and sex-adjusted			Multivariable[A]-adjusted		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
LAFB	2.76	1.68-4.53	<0.001	0.94	0.66-1.34	0.729	0.75	0.43-1.31	0.318
LPFB	1.21	0.17-8.57	0.852	6.96	0.98-49.73	0.053	1.24	0.78-40.19	0.088
$LBBB_{MC}$	7.51	5.10-11.04	<0.001	2.05	1.39-3.02	<0.001	1.55	1.04-2.31	0.032
$LBBB_{STRAUSS}$	6.35	4.07-9.92	<0.001	1.77	1.13-2.77	0.012	1.27	0.80-2.02	0.308
RBBB	6.28	4.42-8.93	<0.001	1.31	0.92-1.87	0.142	1.43	0.98-2.08	0.066
iLBBB	1.02	0.54-1.90	0.960	0.97	0.52-1.81	0.922	0.56	0.29-1.10	0.092
iRBBB	1.75	0.91-3.39	0.095	1.16	0.60-2.24	0.657	1.35	0.69-2.62	0.379
R-R' pattern	1.05	0.73-1.51	0.779	0.94	0.66-1.36	0.750	1.05	0.72-1.52	0.806
Non-specific $IVCD_{MC}$	3.23	1.67-6.24	<0.001	2.76	1.43-5.35	0.003	2.30	1.85-4.49	0.015
Non-specific $IVCD_{STRAUSS}$	4.96	3.02-8.15	<0.001	3.15	1.91-5.18	<0.001	2.87	1.72-4.78	<0.001

CI = Confidence interval; HR = Hazard Ratio; MC = Minnesota definition; [A]Adjusted for: age, sex, hypertension, diabetes mellitus, smoking, BMI, LDL cholesterol, CHD, myocardial infarction, and heart failure.

Interaction analyses showed no interaction between LBBB and the presence of CHD or heart failure associating with the risk of CV or all-cause mortality (P for interaction >0.1). Interaction analyses for RBBB, non-specific IVCD, incomplete blocks and fascicular blocks were also tested similarly and showed no interaction associating with the risk of mortality (P for interaction >0.1) except for non-specific

$IVCD_{STRAUSS}$ (P for interaction = 0.027 for CV mortality, and = 0.006 for all-cause mortality). In age- and sex-adjusted Cox regression analysis, the hazard ratio for CV death for non-specific $IVCD_{STRAUSS}$ was 0.42 (95% CI 0.06–2.98, P = 0.385) for subjects without CHD or heart failure, and 4.30 (95% CI 2.56–7.31, P <0.001) for subjects with CHD or heart failure at the baseline. For overall mortality, the hazard ratio was 0.57 (95% CI 0.18–1.78, P = 0.334) for subjects without CHD or heart failure, and 3.40 (95% CI 2.09–5.54, P <0.001) for subjects with CHD or heart failure at the baseline.

5.2 Relation of Intraventricular Conduction Delay to New-onset Heart Failure and Structural Heart Disease (Study II)

After excluding subjects with an apparent prevalent heart failure or structural heart disease at the baseline health examination, the remaining subjects (n = 6 080) formed the study population for Study II. Clinical characteristics for this population are presented in Table 6. As expected, subjects with LBBB, non-specific IVCD, RBBB and LAFB were older and more often had a prevalent CHD, while LBBB and non-specific IVCD were associated with previous myocardial infarction. Subjects with LAFB presented higher levels of LDL cholesterol.

During 15 years of observation, 7.2 % of the population (n = 440) developed a new-onset heart failure, and 4.7 % (n = 286) developed a novel structural heart disease – in 40.3 % the structural heart disease was accompanied by heart failure. Subjects with LBBB, non-specific IVCD, RBBB, and LAFB had the highest rates of incident heart failure, while for structural heart disease, the highest rates were found in those with LBBB and LAFB (Table 6). More specifically, almost half of the subjects with LBBB (49 %; n = 18) and one third of the subjects with non-specific IVCD (32 %; n = 12) developed a new-onset heart failure, and one fifth (22 %; n = 8) of those with LBBB were diagnosed having a novel structural heart disease over the next 15 years from the health examination.

In the age- and sex-adjusted Cox regression analysis (Table 7), hazard ratio for a new-onset heart failure for LBBB was 3.61 (95% CI 2.14–6.08, P < 0.001), and for non-specific IVCD 4.05 (95% CI 2.00–8.20, P < 0.001). After adjusting for known clinical factors, hazard ratio for a new-onset heart failure for LBBB was 3.29 (95% CI 1.93–5.63, P < 0.001), and for non-specific IVCD 3.53 (95% CI 1.65–7.55, P = 0.001). After controlling for prevalent CV risk factors and diseases, RBBB,

incomplete bundle branch blocks and fascicular blocks were not associated with a novel heart failure during the observation.

In the age- and sex-adjusted Cox regression analysis, hazard ratio for structural heart disease in subjects with LBBB was 3.18 (95% CI 1.56–6.47, P = 0.001). The corresponding hazard ratio in the multivariable adjusted Cox model was 2.60 (95% CI 1.21–5.62, P = 0.015). Non-specific IVCD, RBBB, and other conduction blocks were not associated with a structural heart disease during the study follow-up.

Table 6. Baseline Characteristics for Study II.

	No IVCD (n = 5516) Mean / n (%)	LBBB (n = 37) Mean / n (%)	RBBB (n = 61) Mean / n (%)	Non-specific IVCD (n = 38) Mean / n (%)	LAFB (n = 58) Mean / n (%)	LPFB (n = 8) Mean / n (%)	iLBBB (n = 61) Mean / n (%)	iRBBB (n = 59) Mean / n (%)	R-R' pattern (n = 242) Mean / n (%)
Male (%)	44.2	45.9	63.9	81.6	56.1	75.0	77.2	54.2	48.8
Age (years)	51.5 ± 14.2	70.4 ± 11.6*	68.0 ± 14.7*	57.9 ± 16.6*	64.0 ± 14.2*	38.8 ± 12.2*	52.6 ± 16.3	58.2 ± 14.8*	53.6 ± 14.7
Smoking (current)	1512 (27.6)	7 (18.9)	14 (23.0)	5 (13.2)*	8 (14.0)*	1 (12.5)	18 (31.6)	12 (20.3)	69 (28.5)
LDL cholesterol (mmol/L)	3.7 ± 1.1	3.9 ± 1.1	3.8 ± 1.0	3.6 ± 0.8	4.3 ± 1.4*	3.6 ± 1.0	3.8 ± 0.9	3.8 ± 1.2	3.8 ± 1.1
BMI (kg/m^2)	26.9 ± 4.6	27.4 ± 4.2	26.9 ± 3.8	27.3 ± 3.9	26.7 ± 4.8	23.1 ± 1.6*	28.9 ± 3.7*	26.1 ± 4.1	26.0 ± 4.5*
QRS duration (ms)	91 ±12	155 ±17*	137 ±12*	125 ±8*	95 ±11*	103 ±8*	107 ±6*	95 ±11*	91 ±11*
Hypertension	2525 (46.2)	30 (81.1)*	40 (65.6)*	28 (73.7)*	42 (73.7)*	1 (12.5)	32 (56.1)	31 (52.5)*	112 (46.3)
Diabetes	282 (5.1)	5 (13.5)*	4 (6.6)	3 (7.9)	4 (7.0)	0	3 (5.3)	5 (8.5)	7 (2.9)
Heart murmur	466 (8.5)	7 (18.9)*	13 (21.3)*	8 (21.1)*	7 (12.3)	0	7 (12.3)	5 (8.5)	19 (7.9)
Coronary heart disease	431 (7.9)	17 (45.9)*	17 (27.9)*	11 (28.9)*	10 (17.5)*	0	4 (7.0)	9 (15.3)	17 (7.0)
Myocardial infarction	149 (2.7)	8 (21.6)*	4 (6.6)	10 (26.3)*	3 (5.3)	0	2 (3.5)	3 (5.1)	8 (3.3)
Study endpoints									
Heart failure	347 (6.3)	18 (48.6)*	9 (14.8)*	12 (31.6)*	10 (17.5)*	0	7 (12.3)	8 (13.6)	24 (9.9)
Structural heart disease	241 (4.4)	8 (21.6)*	6 (9.8)	2 (5.3)	7 (12.3)*	0	5 (8.8)	3 (5.1)	13 (5.4)

*P <0.05 for difference compared to No IVCD category.

In the Cox regression analysis of subjects (remaining subpopulation n = 5 557) with no history of heart disease, after adjustment for age and sex, the hazard ratio for a new-onset heart failure in the subjects with LBBB and non-specific IVCD was 3.58

(95% CI 1.59–8.07, P = 0.002) and 5.14 (95% CI 2.26–11.66, P < 0.001), respectively. In corresponding analysis, hazard ratio for a structural heart disease for LBBB was 4.65 (95% CI 1.09–11.34, P = 0.001). When the subjects with heart murmurs were removed from analysis (n = 5 097), the hazard ratio for new-onset heart failure was 4.82 (95% CI 1.98–11.72, P = 0.001) for LBBB and 3.63 (95% CI 1.50–11.47, P = 0.028) for non-specific IVCD. Regarding structural heart disease, the hazard ratio in subjects with LBBB was 5.90 (95% CI 2.17–16.03, P = 0.001).

Altogether, throughout the entire period of observation (including subjects with a prevalent heart failure at the baseline), 60 % (n = 28) of those with LBBB, 42 % (n = 19) of those with non-specific IVCD, and 29 % (n = 22) of those with RBBB had developed heart failure at some point of their life (P <0.001).

Table 7. Adjusted Cox proportional hazard analysis for study (II) endpoints.

	New-onset heart failure			Structural heart disease		
Variable	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age- and gender-adjusted						
LBBB (n = 37)	3.61	2.14-6.08	<0.001	3.18	1.56-6.47	0.001
RBBB (n = 61)	1.12	0.61-2.05	0.717	1.17	0.52-2.64	0.715
Non-specific IVCD (n =38)	4.05	2.00-8.20	<0.001	1.10	0.27-4.44	0.892
LAFB (n = 58)	1.13	0.93-2.19	0.728	1.73	0.82-3.69	0.153
LPFB (n = 8)		no events			no events	
iLBBB (n = 61)	1.82	0.81-4.08	0.148	2.05	0.91-4.62	0.083
iRBBB (n = 59)	0.44	0.11-1.75	0.242	0.97	0.31-3.02	0.953
R-R' pattern (n = 242)	1.38	0.89-2.15	0.153	1.07	0.61-1.86	0.820
Multivariable[A]-adjusted						
LBBB	3.29	1.93-5.63	<0.001	2.60	1.21-5.62	0.015
Non-specific IVCD	3.53	1.65-7.55	0.001			

CI = Confidence interval [A]Adjusted for: age, sex, hypertension, diabetes mellitus, smoking, BMI, LDL cholesterol, CHD, and myocardial infarction.

5.3 Prognostic Implications of QRS duration in Electrocardiographic Left Ventricular Hypertrophy (Study III)

Of the entire study population, ECG-LVH was present in 1 337 (22.2 %; 637 women and 700 men) of the subjects. Among subjects with LVH, men had longer QRS duration than women (mean 96 ms [SD 11 ms] vs. 90 ms [SD 11 ms], P < 0.001 for difference). The majority (69.9 %) of subjects with ECG-LVH had QRS <100 ms whereas 22.7 % had QRS of 100-109 ms and 7.5 % had QRS duration ≥110 ms.

The clinical characteristics of the entire study population stratified by QRS duration in LVH and also among subjects in the normal reference group (with no LVH and QRS <100ms) are presented in Table 8. Briefly, subjects with LVH were older and had more often had a history of CV disease when compared to subjects with LVH. There was no difference in the distribution of CV risk factors between the QRS duration subgroups, but CHD and prior myocardial infarction were more common in subjects with QRS duration ≥110 ms (P < 0.001).

During 15 years of follow up, 19.5 % of subjects died (n = 1 174/6 033), of these 483 (41.1 % of all deaths) due to CV causes. According to unadjusted spline model (Figure 2 on the submitted manuscript), the association between QRS duration in LVH and overall mortality seemed non-linear, with the risk of death increasing after the threshold of 100 ms for QRS duration. Supporting this, adjusting for other clinical factors, subjects with LVH with QRS <100 ms showed no significant difference in overall mortality or in CV mortality when compared to subjects with no LVH and a normal QRS (<100 ms) (hazard ratio 1.11 [95 % CI 0.89-1.38], P = 0.350 for CV mortality and hazard ratio 0.96 [95% CI 0.83-1.11], P = 0.599 for overall mortality). In other words, subjects with a QRS duration <100 ms displayed similar mortality rates whether ECG-LVH was present or not.

When analyzing only subjects with LVH (n = 1 337) and using subjects with normal QRS duration (<100 ms) as a reference group, the risk of CV mortality was significantly higher among subjects with QRS 100–109 ms (hazard ratio 1.38 [95% CI 1.01–1.88], P = 0.045) or with QRS ≥110 ms (hazard ratio 1.74 [95% CI 1.07–2.82], P = 0.025). This same trend was also reflected in the increased risk for overall mortality in these groups (hazard ratio 1.22 [95% CI 0.96–1.55], P = 0.112 for QRS 100–109 ms, and hazard ratio 1.52 [95% CI 1.02–2.25], P = 0.039 for QRS ≥110 ms) (Table 9). While the unadjusted spline model suggested that the lower levels of QRS duration could associate with increased mortality, this was not true after adjustments for age and sex (hazard ratio 0.95 [95% CI 0.66–1.37], P = 0.781 for QRS duration <80ms as compared to QRS duration 80–99 ms).

Table 8. Clinical characteristics and prevalence of comorbidities of the study population (III) classified by ECG-LVH and QRS duration.

	No LVH, QRS <100 ms (n = 3 785)		LVH					
			QRS <100 ms (n = 934)		QRS 100-109ms (n = 303)		QRS ≥ 110ms (n = 100)	
	n /mean	% /(SD)	n /mean	% /(SD)	n /mean	% /(SD)	n /mean	% /(SD)
Male	1 300	34.3	410	43.9*	207	68.3	83	83.0*
Age (years)	51.1	(14.0)	57.9	(15.5)*	54.9	(15.7)	57.0	(16.9)
BMI (kg/m^2)	26.8	(4.8)	26.9	(4.5)	27.4	(4.4)	27.1	(3.8)
Current smoking	845	22.3	148	15.8*	64	21.1	17	17.0
LDL cholesterol (mmol/L)	3.7	(1.0)	3.9	(1.1)	3.7	(1.0)	3.8	(0.9)
QRS duration (ms)	86	(7)	87	(7)	103	(3)	118	(8)
Hypertension	1 545	41.0	616	66.1*	194	64.0	71	71.0
Diabetes mellitus	190	5.0	67	7.2	30	9.9	5	5.0
Coronary Heart Disease	270	7.1	141	15.1*	46	15.2	26	26.0†
Myocardial infarction	81	2.1	49	5.2*	18	5.9	15	15.0†
Heart Failure	51	1.3	41	4.4*	11	3.6	7	7.0
Death								
Cardiovascular	219	5.8	127	13.6*	45	14.9	19	19.0†
All-cause	641	16.9	257	27.5*	86	28.4	32	32.0
Incident Heart Failure	176	3.7	87	9.3*	38	12.5	23	23†

*P <0.05 for difference between subgroups of QRS duration <100 ms with or without LVH.
†P <0.05 for difference between three QRS duration subgroups in LVH.

Among the 5 904 subjects with no heart failure at baseline, 6.5 % of the population (n = 382) developed a new-onset heart failure during the follow-up (5.1 % among normal population and 11.1 % among subjects with LVH, P <0.001). In contrast to the association with mortality, LVH associated with an increased risk of new-onset heart failure even among subjects with a QRS <100 ms (hazard ratio 1.40 [95% CI 1.06–1.86], P = 0.019) when compared to normal population (no LVH and QRS <100 ms).

Table 9. Adjusted Cox proportional hazard analysis for CV and all-cause mortality in subjects with electrocardiographic left ventricular hypertrophy in three QRS duration subgroups.

	Age- and gender-adjusted			Multivariable[A]-adjusted		
	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Cardiovascular Mortality						
QRS duration						
<100 ms	1			1		
100–109 ms	1.39	1.00–1.92	0.048	1.38	1.01–1.88	0.045
≥110 ms	1.91	1.20–3.04	0.007	1.74	1.07–2.82	0.025
All-cause Mortality						
QRS duration						
<100 ms	1			1		
100–109 ms	1.17	0.91–1.51	0.222	1.22	0.96–1.55	0.112
≥110 ms	1.54	1.05–2.24	0.026	1.52	1.02–2.25	0.039
New-onset Heart Failure						
QRS duration						
<100 ms	1			1		
100–109 ms	1.83	1.09–3.06	0.023	2.18	1.32–3.61	0.003
≥110 ms	4.36	2.11–9.02	<0.001	3.39	1.60–7.17	0.001

[A]Adjusted for: age, sex, hypertension, CHD, myocardial infarction, heart failure, diabetes mellitus, smoking, BMI, and LDL cholesterol.

When analyzing only subjects with LVH (n = 1 337) and using subjects with LVH but normal QRS <100ms as a reference group the risk of new-onset heart failure was significantly higher among subjects with QRS 100–109 ms (hazard ratio 2.18 [95% CI 1.32–3.61], P = 0.003) or with QRS ≥110 ms (hazard ratio 3.39, [95% CI 1.60–7.17], P = 0.001).

6 DISCUSSION

6.1 Main Findings of the Study

One of the main findings of this study was that the presence of traditional CV risk factors and CV diseases in Finnish subjects with intraventricular conduction blocks do not vary from those in previously published data from the Western countries. Hypertension, different manifestations of atherosclerosis and heart failure are common in subjects with intraventricular conduction blocks. Within 10 years of the baseline health examination, 47 % of those with LBBB, 40 % of those with non-specific IVCD, and 37 % of those with RBBB had died.

Throughout the over 15-year period of observation only 9 % of those with LBBB, and 20 % of those with RBBB, and 24 % of those with non-specific IVCD remained free of any CV diseases. Non-specific IVCD carried the highest relative risk for CV and overall mortality throughout the entire study observation. LBBB was associated with an increased risk of CV mortality with the risk dependent on the definition of the conduction delay. Overall, the risk of mortality associated with intraventricular blocks was highly dependent on existing CV diseases and their risk factors.

During the observation, almost half of the subjects with LBBB and one third of the subjects with non-specific IVCD developed a new-onset heart failure. The risk of heart failure was independent of a known ischemic heart disease or a previous myocardial infarction. The presence of LBBB was also associated with the incidence of a novel structural heart disease in over 15 years of observation, even after excluding those with a prevalent ischemic heart disease and heart failure.

Individuals with left ventricular hypertrophy are vulnerable to congestive heart failure. In left ventricular hypertrophy, QRS duration carries valuable prognostic information. Even minor increases of QRS duration were associated with a higher risk of CV mortality and novel heart failure, and the risk strongly increased with longer QRS duration.

6.2 Prognostic Implications of Intraventricular Conduction Delays

The Framingham Heart Study (n = 5 209) established a close relation to CV diseases in subjects with bundle branch blocks in late 1970s. New-onset LBBB occurred mostly in subjects with a history of hypertension, coronary heart disease, cardiomegaly, or a combination of these. Throughout the entire period of observation only 11 % of these subjects remained free of clinically apparent CV diseases and 50 % died of CV diseases within 10 years of the onset of LBBB (Schneider et al. 1979). Subsequent studies found the development of LBBB was associated with elderly age (Eriksson et al. 1998) and hypertrophied left ventricle (Peter et al. 1998, Imanishi et al. 2006), even in predominantly healthy pilots (Rabkin et al. 1980).

A high burden of CV diseases was found in subjects with LBBB in the present study. In 1958, Lenègre observed in histopathological studies of the heart that most cases of LBBB are of "mechanical" or ischemic nature, later sustained by Lev (Lev 1961, Lev et al. 1963) and Rosenbaum (Rosenbaum et al. 1968, Rosenbaum 1970). Not surprisingly, LBBB was strikingly associated with CHD and hypertension in our study as approximately 50 % had a prevalent CHD, and over 70 % were hypertensive. This is in line with previous literature as the estimates of CHD associated with LBBB have varied up to 47 % (Schneider et al. 1979, Thrainsdottir et al. 1993, Eriksson et al. 1998, Zhang et al. 2012, Badheka et al. 2013) in the Western epidemiologic studies. Remarkably, in a report from the National Health and Nutrition Examination Survey (n = 8 527) (Badheka et al. 2013), only three patients (5 %) with LBBB had no CHD or clinically equivalent disease.

Throughout the entire period of observation only 9 % of those with LBBB remained free of any CV diseases. The result is in line with prior observation from the Framingham Heart Study, which showed that 11 % of those with a newly-acquired LBBB in the observation and 6 % of those with LBBB in the baseline examination remained free of clinically apparent CV diseases (Schneider et al. 1979). Remarkably, only 9 % of individuals with LBBB remained free of CHD, heart failure, structural heart disease or atrial fibrillation as compared to 35 % of those with RBBB in our study.

In the presence of clinical CHD, LBBB is a harbinger of increased mortality. In a study of adults referred for nuclear exercise testing to evaluate known (over 50 % of patients) or suspected CHD (n = 7 073), patients with LBBB (n = 150) had an increased risk of death as compared to those without LBBB (Hesse et al. 2001). In

patients aged over 55 years with a stable CV disease or diabetes with at least one CV risk factor (n = 9 541), both prevalent (n = 246) and incident (n = 148) LBBB were associated with increased CV and overall mortality, and sudden cardiac death (Sumner et al. 2009). In a large study of patients with a stable CHD (n = 15 609) (Freedman et al. 1987), LBBB (n = 250) was an independent predictor of mortality, and patients with LBBB had more often a multivessel disease. Furthermore, ST-segment and T wave abnormalities as a direct result of changes in the sequence and duration of the ventricular depolarization may obscure the diagnosis of ischemia in a setting of acute myocardial infarction. Historically, an appearance of LBBB was associated with 40 to 50 % in-hospital mortality in the prethrombolytic era (Norris and Croxson 1970, Gould et al. 1972, Hindman et al. 1978, Stephenson et al. 2007). Accordingly, as the proximal left bundle branch has a dual blood supply, a severe two- or three-vessel disease should typically be present in these situations (Frink and James 1973, Nikus et al. 2020). Not surprisingly, LBBB has been associated with a higher incidence of cardiogenic shock even in the era of primary percutaneous coronary intervention (Stenestrand et al. 2004, Widimsky et al. 2012, Brown et al. 2013, Pera et al. 2018). Large comorbidity and myocardial dysfunction are the main explanations for the higher mortality (Stenestrand et al. 2004), though difficulties in identifying acute coronary occlusion in patients with LBBB may have a role at least to some extent. In the present study, approximately 25 % of subjects with LBBB had a prior myocardial infarction.

In the Western population studies, LBBB has been frequently associated with increased mortality. In 1930s it was observed that the mortality from LBBB was 60 % within the first year (Perera et al. 1942). In a retrospective cohort study of Olmsted County with asymptomatic patients with normal left ventricular ejection fraction and no heart disease (Miller et al. 2005), those with LBBB (n = 420) had higher mortality than the age and gender matched controls, and earlier occurrence of CV events than those with RBBB (n = 303). In the Atherosclerosis Risk in Communities study (n = 15 408) (Zhang et al. 2016), those with LBBB (n = 90) had increased rates of overall and CHD mortality. In the Framingham Heart Study, increased risk of death was seen in men but not in women with LBBB (Schneider et al. 1979). Other population studies have also associated LBBB with increased CV death (Eriksson et al. 2005, Badheka et al. 2013). Meanwhile, no relation to mortality was seen among predominantly healthy pilots of the United States Air Force in their forties in 1960s (Rotman and Triebwasser 1975) as LBBB (n = 125) did not increase CV death compared to RBBB, and the prognosis with LBBB (n = 52) was associated with only little demonstrable CV impairment in absence of overt CV disease in

predominantly healthy individuals who were evaluated for life insurance from 1930s to 1940s (Rodstein et al. 1951).

In the current study, in addition to a great burden of CV comorbidities, LBBB was independently associated with increased CV mortality but not overall mortality by the conventional definition. This finding is in line with the literature as some investigators have not observed increased rates of overall mortality either (Hardarson et al. 1987, Fahy et al. 1996, Imanishi et al. 2006, Zhang et al. 2012). Within the observation, 74 % of deceased with LBBB died of CV causes.

The standard ECG criteria for LBBB was challenged 10 years ago. In the current study, the Strauss definition of LBBB (Strauss et al. 2011) was met in 80 % of subjects positive for the conventional LBBB criteria. The result is close to a previous population study (Almer et al. 2015), where the Strauss definition was met in 87% of LBBB patients. To our knowledge, this is the first study to investigate the influence of the definition of LBBB on outcome in a nationally representative general population. In the present study, only the conventional definition of LBBB was independently associated with increased CV mortality after adjustment for known clinical risk factors. The finding is probably explained by the superiority of the Strauss definition to sort out patients with non-specific IVCD from those with a genuine conduction delay in the left bundle branch induced by a conduction disorder. The finding is in line with a previous study with heart failure patients - the results showed that the Strauss definition was significantly better than other definitions of LBBB predicting survival in cardiac resynchronization therapy (CRT) (Jastrzebski et al. 2018). As such, some discrepancy between previous studies may not only account for differences in the diagnostic level of baseline cardiac diseases and the patient populations studied, but also the definition of LBBB used in these studies as the current study elucidated the definition to have impact on prognosis.

The Framingham Heart Study researchers related the natural history of congestive heart failure to a very grave prognosis in 1970s – more than half of the subjects were dead within five years after the incidence of heart failure (McKee et al. 1971). The Swedish Register of Cardiac Intensive Care Study of patients with symptomatic heart failure admitted to a coronary care unit in 1995 to 2003 (n = 21 685) established a very high mortality in patients with LBBB (n = 4 395) – the mortality rates at 1, 5, and 10 years were 32 %, 69 % and 90 %, respectively (Tabrizi et al. 2007). Several other studies also concluded that LBBB is associated with increased mortality rates in heart failure (Baldasseroni et al. 2002, Wang et al. 2008, Abdel-Qadir et al. 2011, Cinca et al. 2013, Lund et al. 2013). In the beginning of the 21st century, several randomized trials demonstrated the benefits of CRT on

mortality and heart failure hospitalizations even in patients with a mild, New York Heart Association functional class I and II systolic heart failure (Rivero-Ayerza et al. 2006, Al-Majed et al. 2011, Selcuk et al. 2011, Linde et al. 2013, Goldenberg et al. 2014). Electrocardiographic inclusion criterion was based on QRS duration, and not on QRS morphology in these studies. Subanalysis of the Multicenter Automatic Defibrillator Implantation Trial with CRT concluded that the response to CRT is highly dependent on the presence of LBBB (Zareba et al. 2011). Thus, the current guidelines of the European Society of Cardiology counsel CRT in patients with symptomatic systolic heart failure and LBBB with class I recommendation (Brignole et al. 2013). In fact, the presence of LBBB on the ECG is superior compared to several echocardiographic parameters of mechanical dyssynchrony and comparative studies showed no correlation between echocardiographic dyssynchrony and clinical response to CRT (Chung et al. 2008).

Considering the grave prognosis in subjects with established heart failure, population studies have evaluated the risk of novel heart failure in those with LBBB. In another report from the Atherosclerosis Risk in Communities study (n = 14 478) (Zhang et al. 2015), LBBB (n = 75) was associated with an increased risk of new-onset heart failure. In men with no angina or dyspnoea on exertion (LBBB n = 46) (Eriksson et al. 2005) and in women without CV disease at baseline (LBBB n = 680) (Zhang et al. 2013) LBBB was associated with an increased risk of heart failure. Another two studies of the Framingham Heart Study cohort reported that participants (n = 1 759) with LBBB (n = 26) were more likely to develop a congestive heart failure than those with a QRS duration <100 ms in their baseline ECG in early 1980s (Dhingra et al. 2006), and the presence of LBBB (n = 7) was especially a risk factor for heart failure with reduced rather than with preserved ejection fraction (Ho et al. 2013). This was also true in the Multi-Ethnic Study of Atherosclerosis (n = 6 664) (O'Neal et al. 2017) as LBBB (n = 22) was associated with the incidence of a systolic heart failure rather than with the incidence of heart failure with preserved ejection fraction. In line with these studies, LBBB was associated with over three-fold risk of developing novel heart failure in our Finnish population, and over one third of the subjects developed heart failure over long period of time.

The presence of LBBB in previous longitudinal studies was also significantly related to underlying cardiac comorbidities also linked to risk of heart failure. In the present study, exclusion of subjects with either previously known or symptomatic heart failure and exclusion of subjects with apparent heart disease at the baseline health examination did not have any significant impact on the results. However, the possibility of underlying silent cardiac conditions, such as reduced left ventricular

function without symptomatic heart failure, cannot be excluded. Nevertheless, in a previous retrospective study of patients with LBBB (n = 94) and preserved ejection fraction (Sze et al. 2017), functional decline measured by change of left ventricular ejection fraction in transthoracic echocardiogram was found in over one third of the patients. Our results are similar demonstrating that over third of all subjects with LBBB but without a prevalent symptomatic heart failure develop symptomatic heart failure over a long period of time.

One of the most likely causes of left ventricular functional decline in LBBB is the associated mechanical dyssynchrony (Vaillant et al. 2013). This is supported by the fact that biventricular pacing, which corrects dyssynchrony, is associated with a reverse in the left ventricular mechanical decline as well as with better outcomes in patients with symptomatic heart failure and LBBB (Linde et al. 2013, Vaillant et al. 2013, Goldenberg et al. 2014). The deleterious effect of LBBB on left ventricular systolic and diastolic function has been established even in subjects without overt heart disease (Grines et al. 1989, Özdemir et al. 2001) and in an animal model (Vernooy et al. 2004) LBBB induced unfavorable ventricular dilation, remodeling and asymmetric hypertrophy in normal hearts. In addition, LBBB induces and aggravates mitral regurgitation by several mechanisms, which prevent normal coaptation of the valve leaflets (Smiseth and Aalen 2019). Recently, studies in patients who developed a persistent LBBB after transcatheter aortic valve implantation procedure confirmed a relation between LBBB and mortality and worsened left ventricular systolic function at 1 and 2-year follow-up (Nazif et al. 2019). These previously referred studies and the results of the current study suggest that LBBB could have a causal role in the development of heart failure.

In the present study, LBBB was associated with an increased risk of novel structural heart disease in the period of observation. The risk was independent of prevalent heart diseases and excluding these subjects did not modify the risk. To our knowledge, this is the first study to address the relation of intraventricular blocks to a novel structural heart disease. While the aggravation of mitral regurgitation may play a role to some extent, LBBB has been previously associated with both ischemic and non-ischemic cardiomyopathies of all forms (Pérez-Riera et al. 2019) which typically remain long clinically silent. In observational studies, term "latent" cardiomyopathy has been applied when the onset of LBBB has been the first presymptomatic objective sign of developing dilated cardiomyopathy before the clinical onset of the disease (Kuhn et al. 1978).

Past epidemiological data from 1950s to 1970s (Rodstein et al. 1951, Rotman and Triebwasser 1975) and clinical experience has shown that isolated LBBB is not

necessarily hazardous in younger population as a result of possible age interactions modulating the association between LBBB and novel heart failure, as younger hearts may be capable to compensate the potential loss of ventricular function. This was shown in a large retrospective cohort study of primary care patients referred for ECG (Rasmussen et al. 2019), where the risk chart depicting 10-year absolute risk of heart failure revealed the risk significantly increasing with age in subjects with LBBB. Unfortunately, due to limited number of subjects with LBBB in our study population, we are unable to present reliable estimates of this statement in our Finnish cohort.

It is also possible that LBBB is only a predisposing factor for subsequent heart failure, and only with additional influences, such as hypertension or ventricular hypertrophy the pump failure will eventually develop. Interestingly, it was demonstrated that subjects with LBBB are hypersensitive to elevated afterload as a moderate elevation of systolic arterial pressure led to marked reductions of left ventricular function (Aalen et al. 2019). This mechanism may explain why hypertensive subjects with LBBB were in greater risk for CV death as compared to hypertensive subjects with ECG-LVH (Li et al. 2008) in the Losartan Intervention For Endpoint Reduction in Hypertension study.

In this study, non-specific IVCD carried the highest relative risk for CV death and new-onset heart failure. The risk of CV mortality was independent of the definition of LBBB, but if defined with the Strauss definition, non-specific IVCD was an independent predictor of overall mortality in this study. This excess risk of all-cause mortality was driven by a strong association with CV mortality. Throughout the study observation, only 24 % of those with non-specific IVCD remained free of any CV diseases, and 80 % of deceased died of CV causes. We believe no prior studies have reported these observations.

In the National Health and Nutrition Examination Survey (n = 8 527) (Badheka et al. 2013) non-specific IVCD (n = 352) was associated with a 40 % increase of CV death but the result was not statistically significant. In the Atherosclerosis Risk in Communities study (n = 15 408) (Zhang et al. 2016), non-specific IVCD (n = 111) was associated with increased all-cause and CV mortality (Zhang et al. 2016) and heart failure (Zhang et al. 2015). While Aro et al. reported that a QRS duration ≥110 ms (n = 67) without LBBB or RBBB was associated with increased risk of arrhythmic death and mortality even in those patients without any suspected heart disease (n = 10 006) (Aro et al. 2011), in a report from the Women's Health Initiative study (n = 66 450) non-specific IVCD (overall n = 122; without CV disease n = 49) was associated with CHD death and overall mortality only in women with a CV disease

at the baseline (n = 52 663) (Zhang et al. 2012). In another study of the same cohort (n = 65 975) (Zhang et al. 2013), non-specific IVCD (n = 117) was a predictor of incident heart failure after excluding patients with prevalent heart failure (self-reported). In the Framingham Heart Study population (n = 1 759) (Dhingra et al. 2006), non-specific IVCD was associated with a two-fold risk of new-onset heart failure in the subjects with this conduction disorder in the baseline ECG (n = 28) in early 1980s. In our study, non-specific IVCD was associated with the incidence of heart failure even after excluding participants with a known ischemic heart disease.

Regional myocardial scarring as a result of fibrosis (Mazzoleni et al. 1975), previous myocardial infarction (Alboni et al. 1976, Flowers et al. 1990), or LVH (Dhingra et al. 2005) has been considered as pathophysiological background factors for non-specific IVCD rather than a discrete lesion in the conduction system. Genetics may also play a role as evidence has emerged that a cumulative burden of QRS prolonging alleles is associated with risk of intraventricular conduction defects (Sotoodehnia et al. 2010). The result was driven by those non-specific IVCD as opposed to those with LBBB or RBBB.

In heart failure, non-specific IVCD was associated with increased mortality and yielded similar, poor prognosis as LBBB (Kashani and Barold 2005, Wang et al. 2008, Kristensen et al. 2020). As opposed to LBBB, dilated cardiomyopathy is less frequent and ischemic heart disease is the most frequent etiology in patients with non-specific IVCD and heart failure (Wilensky et al. 1988, Baldasseroni et al. 2003). This may also explain why LBBB, but not non-specific IVCD was related to a novel structural heart disease in our study as our definition of structural heart disease did not include ischemic cardiomyopathy. In heart failure, those with non-specific IVCD show generalized slow conduction with less, but more heterogenous, dyssynchrony and considerable variation in the location of the latest activated site of the left ventricle related to ischemic endocardial damage, and seem not to derive substantial clinical benefit from CRT (Vassallo et al. 1984, Zareba et al. 2011, Ploux et al. 2013).

RBBB proved to be the most frequent conduction block in our elderly cohort with the prevalence over 7 % in participants aged 85 years or older. This is in line with a report of Swedish men born in 1913 (Eriksson et al. 1998) although both the observations were based on a limited number of subjects. High burden of CV diseases in those with RBBB was observed in this study, and only 20 % remained free of any CV diseases throughout the entire study observation. Our result is in line with the Framingham Heart Study as only 21 % of those with newly-acquired RBBB remained free from clinically apparent CV abnormalities (Schneider et al. 1980).

In the failing heart, RBBB has been a marker of poor prognosis in most studies (McCullough et al. 2005, Wang et al. 2008, Abdel-Qadir et al. 2011, Barsheshet et al. 2011, Cinca et al. 2013, Joseph et al. 2016). Although a QRS duration ≥140 ms was a powerful predictor of CRT response (Cleland et al. 2013), there was no benefit of CRT in those with RBBB in the original retrospective analysis of largest single CRT study (Zareba et al. 2011), and the lack of benefit from CRT in those with non-LBBB QRS morphology was shown in an another meta-analysis of five major CRT studies (Cunnington et al. 2015). "Masquerading" bundle branch block (Rosenbaum 1970, Rosenbaum et al. 1973) that is RBBB with concomitant LAFB simulating LBBB may falsely even prompt CRT recommendation in extreme conditions.

Some authors have shown that RBBB is a marker of impaired prognosis in those with a known or suspected CHD (Hesse et al. 2001, Gaba et al. 2020). In the Copenhagen City Heart Study (n = 18 441) (Bussink et al. 2013), RBBB (n = 166) was associated with an increased risk of mortality, though the prevalence of a stable CHD was not reported. In the National Health and Nutrition Examination Survey (Badheka et al. 2013), RBBB (overall n = 192) was associated with increased CV mortality. However, neither of these studies reported the prevalence of RBBB with bifascicular block pattern which has been associated with a higher CV burden (Schneider et al. 1980, Zhang et al. 2013), and RBBB with LAFB but not isolated RBBB was previously associated with an increased risk of heart failure in two studies (Zhang et al. 2013, 2015). Furthermore, those with a "masquerading" bundle branch block consist a very high-risk subgroup with poor prognosis (Bayés de Luna et al. 1988, Elizari et al. 2013). In most population studies, RBBB has not been associated with increased mortality (Rotman and Triebwasser 1975, Schneider et al. 1980, Fahy et al. 1996, Zhang et al. 2012, 2016). In line, in our Finnish population sample RBBB was not associated with increased mortality, novel heart failure or structural heart disease. However, bifascicular RBBB was associated with increased mortality after adjustment for age and sex and was strongly associated with a known heart failure at the baseline health examination. Although almost 80 % of deceased with RBBB died of CV causes, the risk of mortality seems to be highly dependent on existing CV diseases and risk-factors.

In a previous retrospective study, the presence of LAFB lowered the accuracy to clinically diagnose CHD (Ding et al. 2018). The former is not unexpected as LAFB may both simulate and conceal myocardial infarction (Rosenbaum 1970, Elizari et al. 2007). In a setting of acute myocardial infarction, the presence of a new RBBB with LAFB strongly suggests proximal occlusion of the left anterior descending artery or even left main, and historically mortality reached 80 % in these patients

before the thrombolytic era mostly due to arrhythmia or pump failure (Godman et al. 1971, Gould et al. 1972). In population studies from 1960s and 1970s (Rosenbaum et al. 1968, Yano et al. 1975), isolated LAFB was not associated with excessive mortality. However, while some of the more recent studies have suggested that LAFB may not be as harmless as we have used to think, bearing increased risk of mortality (Mandyam et al. 2013, Nielsen et al. 2014), in the larger study of Nielsen et. al the association with increased risk of overall but not CV mortality seemed to be of only minor clinical relevance as stated by the authors. Although LAFB was a surrogate marker for a greater burden of CV diseases, the mortality was related to the concomitant CV risk factor burden in the present Finnish cohort. LAFB was associated with a seemingly higher risk of new-onset heart failure, but the risk was related to elderly age rather than to LAFB itself as independent prognostic marker. Some overlap between left axis deviation and LAFB is unavoidable, and isolated left axis deviation is a common, age-associated ECG finding not associated with adverse prognosis (Ostrander 1971).

Isolated LPFB is very uncommon and the rarest of all intraventricular blocks. Considering its anatomic location in the less turbulent inflow tract of the left ventricle, the thicker appearance than the anterior fascicle, and the dual blood supply from both the left anterior descending and branches of the right coronary artery (or the left circumflex artery in a left-dominant circulation), it is not unpredictable that the left posterior fascicle is the least vulnerable segment of the whole conduction system, and why LPFB occurs a lot less frequently in hypertensive disease and ventricular dilation than LAFB (Rosenbaum 1968). The definite diagnosis of LPFB cannot be made in the presence of right ventricular hypertrophy, emphysema, a previous large lateral myocardial infarction or extremely vertical heart as a normal variant (Elizari et al. 2007, Pérez-Riera et al. 2018). Thus, the criterion for the diagnosis of LPFB is both clinical and electrocardiographic, and consequently, it is a less specific electrocardiographic entity and is surrounded by a halo of inconsistencies. Moreover, using the rather strict diagnostic criterion requiring a QRS axis oriented around +120° with S1Q3 pattern, many cases of LPFB may be overlooked (Elizari and Chiale 2012). In many cases of the divisions of the conduction system failing one after another before the appearance of a complete AV block, LAFB preceded RBBB and final deathblow was the involvement of the proximal left bundle branch or left posterior fascicle (Elizari et al. 2007). The former is especially true before a development of a complete AV block in Lev's disease in elderly people as a result of degenerative mechanical fibrosis without other signs of cardiac involvement. In the current study, one of the eight subjects with isolated

LPFB died of CV causes and no increased risk of novel heart failure or structural heart disease was found in this study, but the low number of subjects prohibit any definite conclusions to be drawn.

The R-R' pattern and iRBBB may both present in patients with definite heart disease and in those with clinically normal hearts. As incomplete RBBB is a typical finding in pediatric patients with atrial septal defect, symptoms and a fixed split of the second heart sound on auscultation should be excluded in these patients. Other congenital heart diseases producing iRBBB pattern include cyanotic heart defects. For clinicians, a new-onset iRBBB with signs of dyspnea may be a harbinger of life-threating pulmonary embolism due to right ventricular pressure overload (Digby et al. 2015). That said, the presence of R>R' or R<R' may be due to misplacement of the ECG electrodes in the 2nd or 3rd intercostal place, especially when accompanied by a negative P wave in lead V1. Alterations in shape of the chest (pectus excavatum) may expose the pattern (Wachtel et al. 1956). Other benign conditions include late physiologic activation in the right ventricle (Baranchuk et al. 2015). IRBBB has also been associated with exercise-induced physiological left ventricular remodeling and right ventricular enlargement (Kim et al. 2011).

The R-R' pattern and iRBBB proved to be benign findings in this study bearing no increased risk of mortality or heart failure. This result in line with other studies (Rabkin et al. 1981, Liao et al. 1986, Bussink et al. 2013, O'Neal et al. 2015) may strengthen clinicians' belief that the presence of a secondary R wave in the right precordial leads with no clinical suspicion of underlying cardiac pathology seem to be an innocent finding. Epsilon wave in arrhythmogenic right ventricular dysplasia may be mistaken for iRBBB pattern but the typical iRBBB is uncommon in this entity. In some cases, incomplete RBBB should be differentiated from the Brugada pattern with 'coved' or 'saddle-back' ST-segment (Bayés de Luna et al. 2012a), but the syndrome is fortunately rare in Finland.

Incomplete bundle branch blocks were previously associated with slowing of conduction in the infra-Hisian system (Sodi-Pallares et al. 1950, Peñaloza et al. 1961). While in three quarters of cases with iRBBB the right bundle branch was unaffected, iLBBB was almost always associated with significant lesions in the left bundle branch in histopathologic studies and the clinical disease in cases of chronic iLBBB was most often hypertensive or ischemic heart disease (Lenegre 1958, Lev 1960, Lev et al. 1975). In a study of Zhang et al. it was reported that lone iLBBB accounted for 41 % of the CHD deaths and 54 % of all-cause mortality in a combined group of ECG findings in patients with a QRS duration ≥110 ms but <120 ms, and this combined group was associated with increased CHD mortality but not with overall

mortality (Zhang et al. 2016). Our results of the present study differ from the previous findings. However, the reported prevalence of iLBBB pattern in that study greatly differs from the prevalence reported here (12.8 % vs. 1.0 % respectively). In the present study, lone iLBBB was not a predictor of increased mortality or heart failure in the Finnish population.

In previous studies the disappearance of Q wave in left lateral leads was the earliest recognizable sign of iLBBB, and increasing degrees of LBBB were manifested by progressive notching or slurring of the ascending R wave and increase in the QRS duration and voltage, mimicking LVH (Sodi-Pallares et al. 1950, Gardberg and Rosen 1958, Barold et al. 1968). Yet by no means there could be no coexistent hypertrophy as well, and the hypertrophy could well be the cause of the appearance of the block. Thus, a significant overlap probably exists between the ECG diagnosis of LVH and iLBBB, and some authors have questioned the ECG diagnosis and proposed that one should view iLBBB as a variant of LVH with additional conduction delay (Surawicz and Knilans 2008). Interestingly, a prolonged QRS duration in hypertensive patients with ECG-LVH in the setting of aggressive hypertensive therapy predicted overall and CV mortality in the Losartan Intervention For Endpoint Reduction in Hypertension study (Oikarinen et al. 2004).

6.3 Prognostic Implications of QRS duration in Electrocardiographic Left Ventricular Hypertrophy

The Framingham Heart Study researchers identified those with ECG evidence of LVH extremely vulnerable to congestive heart failure in early 1970s (Kannel et al. 1972). But the presence of LVH was related to a very grave prognosis even when unassociated with CHD or heart failure (Kannel et al. 1969, Levy et al. 1996). The risk of every clinical manifestation of CHD, particularly death, was demonstrated critically high in persons with ECG-LVH. Thus, ECG-LVH was established as severe prognostic sign, later sustained by several other studies (Paolo et al. 1998, Mathew et al. 2001, Bang et al. 2017).

LVH is considered as a cornerstone in the CV risk assessment and also as an important marker of end-organ damage in hypertension (Williams et al. 2018, Unger et al. 2020). The higher risk of CV mortality has been observed even in normotensive individuals with ECG-LVH (Brown et al. 2000). But most importantly for clinicians, regression and prevention of ECG-LVH has been associated with reduced risk of future CV events (Mathew et al. 2001, Okin et al. 2004a) independently of baseline

or in-treatment blood pressure levels. Regression of LVH has been related to improvement of diastolic function in hypertensive heart disease (Smith et al. 1986).

A relatively high overall prevalence of ECG-LVH was observed in the present study (22.2% of the population). This could be explained by the use of multiple ECG criteria for the diagnosis. While the prevalence of ECG-LVH may vary from the patient population studied, in the Coronary Heart Disease Study the prevalence of ECG-LVH was 31.3 % (Aro et al. 2011), and in the Copenhagen City Heart Study the prevalence of voltage-only LVH was 23.1 % in men and the overall prevalence of ECG-LVH was 14.5 % (Larsen et al. 2002), and in the Atherosclerosis Risk in Communities Study the prevalence of ECG-LVH by any of the criteria studied was 19.6 % (Okwuosa et al. 2015). In addition, studies have shown that the prevalence of ECG-LVH in a population is largely dependent of the criteria chosen for analysis. A previous study (Porthan et al. 2019) demonstrated that the prevalence of ECG-LVH was 25.1 % if LVH was identified only by one single recently proposed ECG-criterion, Peguero-Lo Presti (Peguero et al. 2017). Additional use of Sokolow-Lyon and Cornell voltage criteria resulted in the overall prevalence of 31.4 % for ECG-LVH in the population in that study.

As expected, the overall prevalence of a clearly prolonged QRS duration ≥110 ms in ECG-LVH was lower (7.5 %) in the general population as demonstrated in this study than what has been previously reported in selected patient cohorts; in a report of the Losartan Intervention For Endpoint Reduction in Hypertension Study cohort dealing with hypertension and heart failure, the prevalence was 21.7 % (Okin et al. 2009). In line, the overall prevalence of a QRS duration ≥100 ms associated with ECG-LVH was lower in our study (30.1 %) than what was reported in an earlier report of veterans from the Palo Alto Veterans Administration Health Care System. In that study the prevalence of a QRS duration >100 ms in ECG-LVH was 43.8 % and the finding was linked to increased CV mortality, but the study sample consisted only of men (Hsieh et al. 2005).

Hypertension was present in 65.9 % of subjects with ECG-LVH in our study. While a minority of subjects with ECG-LVH but no hypertension may have had an underlying structural heart disease resulting in ECG-LVH pattern, it is more plausible that hypertension was not correctly identified in some of the normotensives with ECG-LVH. In the rest of the subjects the ECG-LVH may have been a false-positive finding with no adverse prognostic significance. There was no significant difference in the prevalence of hypertension in relation to QRS duration in ECG-LVH, but CHD and prior myocardial infarction proved to be more prevalent in subjects with ECG-LVH and a QRS duration ≥110 ms.

Previous studies have been dedicated to assess the prognostic relevance of different voltage criteria-based definitions for LVH (Paolo et al. 1998, Hsieh et al. 2005, Cuspidi et al. 2014, Porthan et al. 2015). In the earlier report from the Health 2000 sample, there was no interaction between the two blood pressure categories (normotension and hypertension) and ECG-LVH criteria studied on the risk of CV events (Lehtonen et al. 2016). Of the single ECG-LVH criterion, Sokolow–Lyon voltage performed the best after adjustments in both sexes for predicting CV events (Porthan et al. 2015, Lehtonen et al. 2016), and the Cornell voltage was the only single criterion associated with sudden cardiac death (Porthan et al. 2019). Of the composite criteria, only the composite of Sokolow–Lyon and Cornell voltage associated with sudden cardiac death and CV events for both sexes and seemed valid for clinical use (Porthan et al. 2015, 2019). In the current study, both criteria were used for identifying ECG-LVH.

In the present study, the higher mortality risk associated with QRS duration in ECG-LVH was driven by a strong association with CV mortality, even after adjusting for relevant clinical risk factors including ischemic heart disease. A report from the Losartan Intervention For Endpoint Reduction in Hypertension cohort with hypertensive patients is in line with our results as QRS duration was shown to associate with increased mortality in a mean follow-up of 4.9 years (Oikarinen et al. 2004). Unlike in the previous study, we observed that the association between QRS duration in ECG-LVH and overall mortality seemed non-linear, with increased mortality rates after the threshold of 100 ms for QRS duration. After adjustment for baseline clinical risk factors, subjects with ECG-LVH and QRS duration <100 ms had mortality rates similar to those without ECG-LVH and normal QRS duration. In the review of the literature, we found no prior population-based studies dealing with this issue. Thus, our findings suggest that QRS duration can be used in further risk stratification in subjects with ECG-LVH.

Longer QRS duration has been previously recognized as a specific indicator of left ventricular dysfunction (Murkofsky et al. 1998). In the Losartan Intervention For Endpoint Reduction in Hypertension study cohort, the risk of incident heart failure was observed only in hypertensive patients with a QRS duration ≥110 ms in a mean follow-up of 4.7 years (Okin et al. 2009). In the present study, unlike the risk of mortality, the risk of novel heart failure persisted even in subjects with ECG-LVH and normal QRS duration (<100 ms) when compared to the subjects with no LVH and QRS <100 ms. The risk increased with longer QRS duration, and QRS ≥110 ms was associated with a three-fold risk of developing heart failure in subjects with ECG-LVH throughout the over 15-year period of observation in the present study.

Our study does not provide explanatory pathophysiologic mechanisms for the observed associations between ECG-LVH and QRS duration. One possible pathophysiological mechanism for the relation between QRS duration and the increased risk of mortality and the risk of developing a novel heart failure may be related to left ventricular mass. Prolonged QRS has been shown to correlate with increased left ventricular mass (Krumholz et al. 1993, Oikarinen et al. 2004, Dhingra et al. 2005, Ilkhanoff et al. 2012), and previous study findings have established a linear relationship between left ventricular mass and CV mortality (Casale et al. 1986, Levy et al. 1990, Koren et al. 1991, Giuseppe et al. 2000, Gardin et al. 2001). In a Swedish cohort of elderly men, no obvious cut-off level for prediction of total mortality was found as mortality seemed to increase linearly with left ventricular mass (Sundströ̈m et al. 2001). In the Cardiovascular Health Study population of individuals aged over 65 years with a normal left ventricular ejection fraction at the baseline (Drazner et al. 2004), increased left ventricular mass was identified as a risk factor for the development of a depressed left ventricular systolic function within five years. In the Multi-Ethnic Study of Atherosclerosis (Ilkhanoff et al. 2012), QRS duration ≥100 ms was associated with increased incidence of heart failure, but the risk was attenuated to non-significance after adjustment for magnetic resonance imaging measures of left ventricular structure, suggesting that prolonged QRS duration is a potentially useful marker to detect left ventricular remodeling that may predispose to heart failure.

However, in the review of Aro et al. the authors concluded that ECG-LVH may be a distinct entity to LVH detected by imaging methods, and these two entities may provide different prognostic information (Aro and Chugh 2016). Indeed, ECG-LVH is predictive of future CV events independently of echocardiography findings (Williams et al. 2018). In the analysis of Oregon Sudden Unexpected Death Study (Narayanan et al. 2014), ECG-LVH was a predictor of sudden cardiac arrest even after adjustment for echocardiographic LVH. An earlier report from a Swedish sample (Sundströ̈m et al. 2001) also provided intriguing findings. Although by assessing echocardiographic LVH for subjects with no ECG-LVH another 16 % of total deaths could be predicted, another 18 % of all deaths could be predicted by assessing ECG-LVH if echocardiography showed no LVH. In that study, echocardiographic LVH and ECG-LVH predicted mortality independent of each other. As such, the mortality differences may not be only related to impaired mechanical pump function. Changes in myocardial depolarization result in changes of myocardial repolarization, facilitating electrical re-entry in a vulnerable phase for potential life-threating tachyarrhythmias. This predispose to such re-entry in LVH

may be a manifestation of changes in tissue architecture including increased extracellular myocardial fibrosis and increased gap junctional resistance and nonuniform anisotropic coupling at the cellular level (Cooklin et al. 1997, McIntyre and Fry 1997, Aro and Chugh 2016).

Furthermore, although a normotensive subject without ECG-LVH may well have echocardiographic LVH, the Swedish study showed that no more total or CV deaths could be predicted by assessing echocardiographic LVH for normotensive subjects negative for ECG-LVH and thus is of low prognostic importance and hardly motivates an echocardiographic examination (Sundström et al. 2001). Incorporation of ECG-LVH with elevated cardiac biomarkers (e.g. N-terminal pro–B-type natriuretic peptide) may further aid in the risk prediction and identification of malignant subphenotype of LVH with high risk of progression to heart failure (Neeland et al. 2013).

6.4 Limitations

An observational study cannot, by definition, give conclusive information about causality. Absence of imaging data, such as echocardiography, is also a study limitation typical of a large population study. Some of the subjects may have had an underlying structural heart disease that was not evident in the clinical examination but caused LBBB or prolongation of QRS duration in their 12-lead ECGs.

ECGs were recorded only once and no data on the progression of ECG changes was available for a reasonable number of patients with intraventricular conduction blocks or prolonged QRS duration as many of them deceased within 10 years. We also lack data related to possible changes in medication during follow-up potentially affecting left ventricular mass.

A number of patients with some of the intraventricular blocks, especially LPFB, is too small to draw any definite conclusions.

Although a nationwide study would be considered as a strength, the incidence of CHD is higher in the Eastern Finland and CHD mortality is approximately one fifth higher there. Our results may also not be transferable to other populations.

7 CONCLUSIONS

In a nationally representative population study of predominantly middle-aged subjects with long-term follow-up, intraventricular blocks proved to have different prognostic implications and association with mortality and heart failure depending on the type of IVCD. The principal findings and conclusions are as follows:

1. Non-specific IVCD carried the highest relative risk for mortality, independently of several clinical risk factors. This excess risk of all-cause mortality was driven by a strong association with CV mortality, while the prognosis of RBBB, incomplete bundle branch blocks and fascicular blocks was related to the presence or absence of classical CV risk factors and existing CV diseases as none of these were independently associated with excess mortality in the general population.

2. The definition of LBBB has influence on outcome in general population. LBBB by conventional criteria was associated with increased rates of CV mortality independently of several baseline variables, but the risk of mortality was attenuated by the definition of the conduction delay. Thus, the definition of LBBB should be taken into account in studies assessing the clinical significance of LBBB.

3. Both non-specific IVCD and LBBB carried a high risk of new-onset heart failure throughout the study observation. The risk was independent of several CV risk factors and CV diseases, and even observed in individuals free of a known ischemic heart disease. LBBB also carried a risk of novel structural heart disease during the observation. RBBB, incomplete bundle branch blocks and fascicular blocks were not associated with excess risk of new-onset heart failure or novel structural heart in the long-term follow-up.

4. In ECG-LVH, the QRS duration was prolonged (≥100 ms) in 30.1 % and clearly prolonged (≥110 ms) in 7.5 % of the subjects. There was no difference in distribution of modifiable CV risk factors in relation to QRS duration in ECG-LVH though CHD was more common in those with QRS duration ≥110 ms.

5. The risk of excess mortality and risk of novel heart failure strongly increases along longer QRS duration in ECG-LVH, independently of prevalent ischemic heart disease. Even QRS duration within normal limits possesses a risk of new-onset heart failure in ECG-LVH as compared to those without ECG-LVH.

For clinical implications, the presence of non-specific IVCD, LBBB or prolonged QRS duration in combination of ECG-LVH should alert physicians to perform careful cardiac evaluation even in the absence of CV symptoms and ischemic heart disease. Hence, these patients could benefit from strict treatment of CV risk factors. On the other hand, right-sided ventricular conduction delays, incomplete bundle branch blocks and fascicular blocks on ECG with no clinical suspicion of underlying cardiac pathology seem to be innocent findings with no excess risk of mortality or heart failure in the general population.

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PUBLICATIONS

PUBLICATION I

Long-term outcome of intraventricular conduction delays in the general population

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ORIGINAL ARTICLE

WILEY

Long-term outcome of intraventricular conduction delays in the general population

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Abstract

Background: Previous population studies have presented conflicting results regarding the prognostic impact of intraventricular conduction delays (IVCD).

Methods: We studied long-term prognostic impact and the association with comorbidities of eight IVCDs in a random sample of 6,299 Finnish subjects (2,857 men and 3,442 women, mean age 52.8, *SD* 14.9 years) aged 30 or over who participated in the health examination including 12-lead ECG. For left bundle branch block (LBBB) and non-specific IVCD (NSIVCD), two different definitions were used.

Results: During 16.5 years' follow-up, 1,309 of the 6,299 subjects (20.8%) died and of these 655 (10.4%) were cardiovascular (CV) deaths. After controlling for known clinical risk factors, the hazard ratio for CV death, compared with individuals without IVCD, was 1.55 for the Minnesota definition of LBBB (95% confidence interval 1.04–2.31, $p = .032$) and 1.27 (95% confidence interval 0.80–2.02, $p = .308$) for the Strauss' definition of LBBB. Subjects with NSIVCD were associated with twofold to threefold increase in CV mortality depending on the definition. While right bundle branch block, left anterior fascicular block and incomplete bundle branch blocks were associated with seemingly higher mortality, this was no longer the case after adjustment for age and sex. The presence of R-R' pattern was not associated with any adverse outcome.

Conclusions: In a population study with long-term follow-up, NSIVCD and Minnesota definition of LBBB were independently associated with CV mortality. Other IVCDs had no significant impact on prognosis. The prognostic impact of LBBB and NSIVCD was affected by the definition of the conduction disorder.

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KEYWORDS
bundle branch block, electrocardiography, intraventricular conduction delay, population study, prognosis

1 | INTRODUCTION

The clinical significance of various intraventricular conduction delays (IVCD) depends on the type of the conduction disorder and on the studied patient population. Both right (RBBB) and left bundle branch blocks (LBBB) are associated with adverse outcome in subjects with overt cardiovascular disease (CV; Wang et al., 2008; Zhang et al., 2012). In subjects with IVCDs without other evidence of cardiac disease (isolated bundle branch block), published reports show conflicting results. Some authors showed that RBBB was associated with increased all-cause mortality, while other investigators found no effect on outcome (Bussink et al.., 2013; Haataja et al., 2015). The results of studies evaluating the prognostic impact of LBBB on all-cause mortality in subjects without known CV disease are also somewhat conflicting (Haataja et al., 2015; Imanishi et al., 2006; Schneider, Thomas, Kreger, McNamara, & Kannel, 1979), and even the standard electrocardiographic (ECG) criteria for LBBB have been challenged (Strauss, Selvester, & Wagner, 2011). On the other hand, non-specific IVCD (NSIVCD) is considered as an ECG marker of adverse outcome due to its potential association with structural heart disease (Eschalier et al., 2015; Haataja et al., 2015). The effect of the ECG definitions of LBBB and NSIVCD on outcome has not been reported in prior population studies.

Left anterior fascicular block (LAFB) is usually regarded as a conduction disorder without clinical significance if encountered in asymptomatic individuals (Elizari, Acunzo, and Ferreiro, 2007). Isolated left posterior fascicular block (LPFB) is a rare conduction disorder with no clear consensus on prognostic significance without CV disease (Pérez-Riera et al., 2018). Previous scientific literature does not provide much information about the prevalence or prognostic significance of incomplete bundle branch blocks in individuals apparently free of CV disease. Somewhat surprisingly, one previous study found that incomplete RBBB (iRBBB) was associated with increased all-cause and CV mortality (Haataja et al., 2015). Only two prior population studies have assessed the clinical significance of incomplete LBBB (iLBBB) and found no relation to CV mortality (Haataja et al., 2015); (Tervahauta, Pekkanen, Punsar, & Nissinen, 1996).

While the current guidelines suggest the use of transthoracic echocardiography to rule out structural heart disease in isolated LBBB, the recommendation is less stringent in patients with conduction disorders other than LBBB (Kusumoto et al., 2018). These recommendations are based on observational evidence, and due to the limited data, there is no consensus on the need of follow-ups after the initial screening.

The purpose of this study was to explore the prevalence, relation to CV comorbidities and prognostic significance of IVCDs in a predominantly Caucasian general population during a total follow-up time of 16.5 years.

2 | METHODS

2.1 | Study population

The Health 2000 is a major Finnish health examination survey. The survey was carried out in 2000–2001, and a representative stratified random cluster sample of the Finnish population was examined. For the population aged ≥ 80 years, the sampling probability was twice as high as among those <80 years. The implementation of the survey was described in detail elsewhere (Heistaro, 2000).

The Health 2000 sample comprised random sample of 8 028 individuals (3 637 men and 4 391 women) aged 30 or older, of whom 79% (6 354 individuals; 2 876 men and 3 478 women) participated in the health examination. After a home interview, a comprehensive health examination, including questionnaires, measurements (e.g., blood pressure and resting ECG), and physician's physical examination, was performed. The National Care Register for Health Care and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data. The study protocol of the Health 2000 survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

2.2 | Definition of coronary heart disease and myocardial infarction

Classification as coronary heart disease (CHD) required at least one of the following: diagnosis of myocardial infarction (MI) and/or angina pectoris during the field health examination by a physician, large Q waves in the resting ECG, hospitalization for CHD (International Classification of Diseases [ICD]-8 or ICD-9 codes 410–414 or ICD-10 codes I20–I25), a history of coronary revascularization procedure, the right to drug reimbursements for CHD, or the use of nitroglycerine combined with an anticoagulant, acetyl salicylic acid, or beta-blocker. The Finnish Care Register for Health Care has been shown to be valid in identifying major CHD events (Pajunen et al., 2005).

Classification for MI required either a clinical diagnosis of old MI by the examining physician, large Q waves in the resting ECG, or a previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21–I22). Old MI was defined as a positive history of the condition in the medical records or old MI in the ECG, or typical self-reported history of MI treated in hospital. Large Q waves

indicating probable previous MI included Minnesota codes (MC) 1.1–1.3.

2.3 | Heart failure, stroke, and peripheral artery disease

Heart failure (HF) classification required a clinical diagnosis by the examining physician and either a previous discharge diagnosis of HF (ICD-8 code 4,270, ICD-9 code 428, or ICD-10 code I50) or the right to drug reimbursements for HF. The classification for stroke required one or more discharge diagnoses of stroke (ICD-8 codes 430–431, 433–434, ICD-9 codes 430–434, or ICD-10 codes I60, I61, I63). Classification for peripheral arterial disease (PAD) required a clinical diagnosis by the examining physician or previous hospitalization for PAD.

2.4 | Other measurements, definitions, and laboratory tests

The health examination included measurements of height, weight, body mass index (BMI), and waist circumference. Blood pressure (BP) was measured with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller) from the right arm. Hypertension was defined as a clinic BP ≥ 140/90 mmHg or right to drug reimbursements for hypertension. Diabetes mellitus was defined as a serum glucose level of 7.0 mM or greater or a history of the use of oral hypoglycemic agents or insulin therapy. Smoking was defined as frequent use of tobacco products. Laboratory tests included measurements for high-density lipoprotein cholesterol, total cholesterol, triglyceride, and serum glucose. Low-density lipoprotein cholesterol was calculated with the Friedewald formula.

2.5 | ECG registration and analysis

Standard 12-lead ECGs were recorded in the resting supine position by MAC 5000 recorders (Marquette Hellige) and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige). All ECGs were read, and the computerized diagnoses and measurements corrected if needed, by a physician experienced with ECG before being stored in the database. ECG was recorded and printed using a paper speed of 50 mm/s. The maximal filter setting of the system (150 hertz) was used. The Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators who were blinded to the clinical data of the subject. ECGs were obtained successfully in 6 318 individuals (99%) who attended the health examination. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding scheme (Pekkanen, Nissinen, Puska, Punsar, & Karvonen, 1989). The electrical recordings were analyzed by means of Magellan software program (Marquette Electronics Inc.). Nineteen ECGs were rejected owing to data lost in further processes, leaving 6 299 ECGs for analysis.

2.6 | Follow-up

Mortality information until the end of December 2015 (total follow-up time 16.5 years, median 15.9 years) was gathered by linking the personal identity code from the Health 2,000 Survey database to the Care Register for Health Care and the Causes of Death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens in Finland and nearly 100% abroad. Mortality information was available for all subjects.

2.7 | Exclusion criteria

There was no exclusion of subjects based on ECG findings. Final analysis was performed with 6 299 subjects: 3 442 women and 2 857 men.

2.8 | Definition of IVCDs

For the identification of different intraventricular conduction delays, both Minnesota codes and measurements based on the Magellan software program were used. Six of the conduction delays were classified according to the respective Minnesota classes: $LBBB_{MC}$ (code 7–1), RBBB (code 7–2), iRBBB (code 7–3), non-specific $IVCD_{MC}$ (code 7–4), the R-R' pattern in either of leads V1, V2 with R' amplitude ≤R (R-R') (code 7–5), and iLBBB (code 7–6). Two different definitions for LBBB and NSIVCD were used. The Strauss' definition of LBBB was used ($LBBB_{STRAUSS}$) to identify subjects with "strict" LBBB (Strauss et al., 2011). The Strauss definition of LBBB includes a QRS duration ≥140 ms for men and ≥130 ms for women, along with mid-QRS notching or slurring in ≥2 contiguous leads. ECGs not meeting the criteria for $LBBB_{STRAUSS}$ were defined as non-specific $IVCD_{STRAUSS}$. For LAFB, we used the following definition: frontal QRS axis between −30° and −90°, rS configuration in II, III, and aVF, and qR configuration in aVL, with a QRS duration <120 ms. LPFB was defined as frontal QRS axis > 120°, lead I rS configuration, leads II, III, and aVF qR configuration, and no pathological Q waves in leads II, III, aVF. The accuracy of the classification was checked by manual ECG analysis by three of the investigators (JR, PH, and KN). The classifications proved to be accurate.

2.9 | Statistical analyses

The prevalence of IVCDs was established in six age groups: 30–44, 45–54, 55–64, 65–74, 75–84, and 85 or older. Proportions were

compared with the chi-square test or Fisher's exact test. The complex sampling design was taken into account by correcting for the oversampling of subjects over 80 years of age. Data were categorized into ten groups according to the presence and type of IVCD (eight IVCDs with two definitions for LBBB and NSIVCD). CV death was defined as primary and all-cause death as secondary study endpoint. Survival to each endpoint was assessed using the Kaplan–Meier method. Age and sex adjustments were included. Hazard ratios (HR) were calculated by univariate and multivariate Cox regression model analysis. Multivariate analysis included the following parameters: age, sex, CHD, MI, HF, New York Heart Association class, hypertension, diabetes mellitus, smoking, BMI, and low-density lipoprotein cholesterol. Death from non-CV causes was considered as a competing event to CV death. To take into account this competing risk, a model according to the method of Fine and Gray subhazards model was applied. Statistical significance was based on $p < .05$.

3 | RESULTS

Figure 1 (based on Supplemental Material) illustrates the prevalence of IVCDs divided by the six age groups. The prevalence of LAFB, LBBB, non-specific $IVCD_{STRAUSS,}$ and RBBB clearly increased with age, while for the other conduction delays, there was no clear age association. $LBBB_{STRAUSS}$ criteria were met in 80% of subjects positive for $LBBB_{MC}$.

Table 1 and Supplemental Material show the baseline and clinical characteristics. R-R', iRBBB, and LPFB had no clear relationship with CV diseases, while in subjects with LBBB and RBBB, there was a high prevalence of CV diseases and diabetes. The other IVCDs showed varied associations with risk factors and studied disease. LAFB, LBBB, NSIVCD, and RBBB were most strongly associated with HF, while LBBB, RBBB, NSIVCD, LAFB, and iLBBB were associated with the different manifestations of atherosclerosis.

3.1 | Outcome

During 16.5 years' follow-up, 1,309 of the 6,299 subjects (20.8%) died and of these 655 (10.4%) were CV deaths. Table 2 shows the unadjusted mortality rates for the different IVCDs. For all-cause mortality, subjects with LBBB, RBBB, LAFB, NSIVCD, iLBBB, and iRBBB had the highest mortality rates, while for CV deaths, the highest rates were found in the LBBB, RBBB, NSIVCD, and LAFB categories.

In the age- and sex-adjusted Cox regression analysis (Table 2), the HR for CV death for $LBBB_{MC}$ was 2.05 (95% confidence interval 1.39–3.02, $p < .001$), for $LBBB_{STRAUSS}$ 1.77 (1.13–2.77, $p = .012$), for non-specific $IVCD_{MC}$ 2.76 (1.43–5.35, $p = .003$) and for non-specific $IVCD_{STRAUSS}$ 3.15 (1.91–5.18, $p < .001$). In the multivariate-adjusted Cox model, $LBBB_{MC}$ and NSIVCD regardless of the definition retained their statistical significance to predict CV death.

$LBBB_{MC}$, but not $LBBB_{STRAUSS}$, was associated with all-cause mortality in age- and sex-adjusted Cox regression analysis (1.49, 1.07–2.07, $p = .018$), but not after multivariate adjustment. Subjects with non-specific $IVCD_{STRAUSS}$ were associated with all-cause mortality both in age- and sex-adjusted (2.07, 1.33–3.23, $p = .001$), and multivariate-adjusted (2.01, 1.27–3.18, $p = .003$) Cox regression analysis. Subjects with non-specific $IVCD_{MC}$ displayed no relation to increased all-cause mortality.

In the Cox regression analysis of subjects with history of heart disease (CHD, previous MI, or HF), after controlling for known clinical risk factors, subjects with NSIVCD, $LBBB_{MC,}$ and iRBBB were associated with all-cause and CV mortality, and subjects with RBBB were associated with CV mortality (see Supplemental Material).

4 | DISCUSSION

The main findings of the present study were that NSIVCD and $LBBB_{MC}$, but not $LBBB_{STRAUSS}$, were associated with increased CV mortality after adjustment for baseline cardiac comorbidities. Regarding mortality, $LBBB_{STRAUSS}$ identifies subjects with seemingly

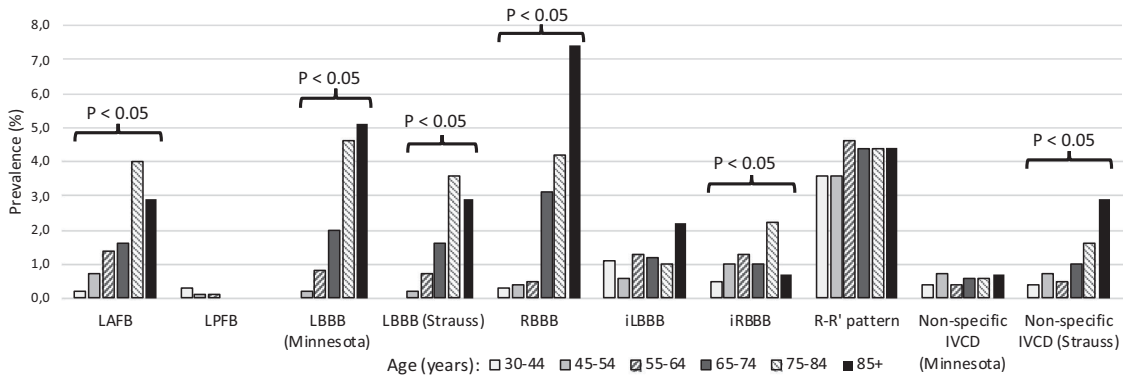

FIGURE 1 Prevalence of intraventricular conduction delays in six age groups; the significances of the difference within the age groups are shown (chi-square test). iLBBB, incomplete LBBB; iRBBB, incomplete RBBB; IVCD, intraventricular conduction delay; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block

TABLE 1 Clinical characteristics and mortality of the study population according to presence of intraventricular conduction delay

	Intraventricular conduction delay										
	No IVCD ($n = 5\,587$)	LAFB ($n = 69$)	LPFB ($n = 8$)	$LBBB_{MC}$ ($n = 59$)	$LBBB_{STRAUSS}$ ($n = 47$)	RBBB ($n = 75$)	iLBBB ($n = 66$)	iRBBB ($n = 61$)	R-R' pattern ($n = 249$)	Non-specific $IVCD_{MC}$ ($n = 33$)	Non-specific $IVCD_{STRAUSS}$ ($n = 45$)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Smoking (current)	1,549 (27.2)	10 (14.7)*	1 (12.5)	9 (15.3)*	8 (17.0)	15 (20.0)	18 (29.5)	12 (19.7)	71 (28.5)	6 (18.2)	7 (15.6)
Hypertension	2,671 (46.9)	50 (73.5)*	1 (12.5)	47 (79.7)*	37 (78.7)*	50 (66.7)*	35 (57.4)	31 (50.8)	115 (46.2)	22 (66.7)*	32 (71.1)*
Diabetes mellitus	324 (5.7)	6 (8.8)	0	10 (16.9)*	8 (17.0)*	9 (12.0)*	4 (6.6)	6 (9.8)	7 (2.8)*	2 (6.1)	4 (8.9)
Heart failure	118 (2.1)	9 (13.2)*	0	12 (20.3)*	9 (19.1)*	13 (17.3)*	3 (4.9)	1 (1.6)*	5 (2.0)	3 (9.1)*	6 (13.3)*
NYHA class II-IV	355 (6.2)	10 (14.7)*	0	27 (46.6)*	19 (41.3)*	16 (21.6)*	6 (9.8)	8 (13.3)	10 (4.0)	5 (15.2)	13 (28.9)*
Stroke	213 (3.7)	6 (8.8)*	0	8 (13.6)*	4 (8.5)	6 (8.0)	1 (1.6)	1 (1.6)	14 (5.6)	5 (15.2)*	9 (20.0)*
Peripheral artery disease	82 (1.4)	2 (2.9)	0	6 (10.2)*	4 (8.5)*	3 (4.0)	1 (1.6)	5 (8.2)	4 (1.6)	3 (9.1)*	5 (11.1)*
Coronary heart disease	529 (9.3)	14 (20.6)*	0	31 (52.5)*	24 (51.1)*	25 (33.3)*	8 (13.1)	10 (16.4)	20 (8.0)	10 (30.3)*	17 (37.8)*
Myocardial infarction	189 (3.3)	4 (5.9)*	0	17 (28.8)*	11 (23.4)*	6 (8.0)*	5 (8.2)*	3 (4.9)	10 (4.0)	9 (27.3)*	15 (33.3)*
Death											
All-cause	1,097 (19.2)	31 (45.6)*	1 (12.5)	37 (62.7)*	27 (57.4)*	45 (60.0)*	14 (23.0)*	21 (34.4)*	53 (21.3)	10 (30.3)	20 (44.4)*
Cardiovascular	435 (7.6)	17 (24.6)*	1 (12.5)	27 (45.8)*	20 (42.6)*	33 (44.0)*	10 (15.2)	9 (14.8)	31 (12.4)	9 (27.3)*	16 (35.6)*
Medication											
ACI/ARB	454 (8.0)	8 (11.8)	0	15 (25.4)*	12 (25.5)*	5 (6.7)	5 (8.2)	9 (14.8)*	17 (6.8)	8 (24.2)*	11 (24.4)*
Beta adrenergic blockers	794 (13.9)	15 (22.1)	1 (12.5)	25 (42.4)*	20 (42.6)*	20 (26.7)*	7 (11.5)	15 (24.6)*	40 (16.1)	12 (36.4)*	17 (37.8)*
Calcium channel blockers	313 (5.5)	4 (5.9)	0	9 (15.3)*	7 (14.9)*	10 (13.3)*	1 (1.6)	4 (6.6)	18 (7.2)	7 (21.2)*	9 (20.0)*
Antithrombotics	513 (9.0)	17 (25.0)*	0	19 (32.2)*	12 (25.5)*	20 (26.7)*	10 (16.4)	14 (23.0)*	26 (10.4)	11 (33.3)*	18 (40.0)*
Diuretics	391 (6.9)	9 (13.2)	0	16 (27.1)*	9 (19.1)*	19 (25.3)*	7 (11.5)	6 (9.8)	17 (6.8)	7 (21.2)*	14 (31.1)*
Statin	348 (6.1)	3 (4.4)	0	7 (11.9)	5 (10.6)	6 (8.0)	4 (6.6)	5 (8.2)	12 (4.8)	4 (12.1)	6 (13.3)*

Abbreviations: ACI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; iLBBB, incomplete LBBB; iRBBB, incomplete RBBB; IVCD, intraventricular conduction delay; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; MC, Minnesota definition; NYHA, New York Heart Association; RBBB, right bundle branch block; Strauss, Strauss definition.

*$p < .05$

TABLE 2 Adjusted Cox proportional hazard analysis for cardiovascular mortality according to intraventricular conduction delay

	Cardiovascular mortality								
	Unadjusted			Age- and sex-adjusted			Multivariate*-adjusted		
Intraventricular conduction delay	Hazard ratio	95% CI	*p* Value	Hazard ratio	95% CI	*p* Value	Hazard ratio	95% CI	*p* Value
LAFB	2.76	1.68–4.53	<.001	0.94	0.66–1.34	.729	0.75	0.43–1.31	.318
LPFB	1.21	0.17–8.57	.852	6.96	0.98–49.73	.053	1.24	0.78–40.19	.088
$LBBB_{MC}$	7.51	5.10–11.04	<.001	2.05	1.39–3.02	<.001	1.55	1.04–2.31	.032
$LBBB_{STRAUSS}$	6.35	4.07–9.92	<.001	1.77	1.13–2.77	.012	1.27	0.80–2.02	.308
RBBB	6.28	4.42–8.93	<.001	1.31	0.92–1.87	.142	1.43	0.98–2.08	.066
iLBBB	1.02	0.54–1.90	.960	0.97	0.52–1.81	.922	0.56	0.29–1.10	.092
iRBBB	1.75	0.91–3.39	.095	1.16	0.60–2.24	.657	1.35	0.69–2.62	.379
R-R' pattern	1.05	0.73–1.51	.779	0.94	0.66–1.36	.750	1.05	0.72–1.52	.806
Non-specific $IVCD_{MC}$	3.23	1.67–6.24	<.001	2.76	1.43–5.35	.003	2.30	1.85–4.49	.015
Non-specific $IVCD_{STRAUSS}$	4.96	3.02–8.15	<.001	3.15	1.91–5.18	<.001	2.87	1.72–4.78	<.001

Abbreviations: CI, confidence interval; iLBBB, incomplete LBBB; iRBBB, incomplete RBBB; IVCD, intraventricular conduction delay; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; MC, Minnesota definition; RBBB, right bundle branch block; Strauss, Strauss definition.

*Adjusted for age, sex, coronary heart disease, myocardial infarction, heart failure, NYHA class, hypertension, diabetes mellitus, smoking, body mass index, and low-density lipoprotein cholesterol.

lower risk for death when compared to the $LBBB_{MC}$ definition. However, subjects with NSIVCD had significantly worse outcome when compared to subjects with LBBB by the Strauss' criteria. LAFB and iLBBB displayed relationship with mortality in unadjusted Cox regression analysis but neither impaired the prognosis after adjustments for age and sex.

The Framingham Heart Study ($n = 5,209$) described a close relation to CV diseases in LBBB patients (Schneider et al., 1979). In the present study, there was a high prevalence of CV diseases in subjects with LBBB, and 52.5% of the subjects had known CHD. In our subgroup analyses, LBBB was associated with higher CV mortality in subjects with history of heart disease. The Reykjavik Health Survey ($n = 17,489$; Hardarson et al., 1987) and the follow-up study of atomic bomb survivors in Hiroshima and Nagasaki ($n = 17,361$; Imanishi et al., 2006) reported no increased all-cause mortality in subjects with LBBB. In the Framingham Heart study, multivariate risk analysis indicated that the risk for incident CHD morbidity remained significant in women but not in men (Schneider et al., 1979). In the Women's Health Initiative study ($n = 68,133$; Zhang et al., 2012), LBBB was associated with increased CV mortality in patients without known CV disease. Similarly, in the Primary Prevention Study from Gothenburg ($n = 7,392$), LBBB was a marker of adverse prognosis in symptom-free men (Eriksson, Wilhelmsen, & Rosengren, 2005). Thus, LBBB may be a marker of a slowly progressing disease that not only affects the conduction system but also the myocardium itself (Eriksson et al., 2005). The differences in study results may be due to differences in the diagnostic level of baseline cardiac diseases and also to the patient populations studied.

$LBBB_{STRAUSS}$ criteria were met in 80% of subjects positive for $LBBB_{MC}$. The result is close to a previous population study (Almer et al., 2015), where the Strauss' definition was met in 87% of LBBB patients. To our knowledge, this is the first study to investigate the influence of the definition of LBBB and NSIVCD on outcome in a nationally representative population. In the present study, $LBBB_{STRAUSS}$ was associated with lower risk of death compared to $LBBB_{MC}$. The finding is probably explained by the superiority of the $LBBB_{STRAUSS}$ definition to sort out patients with NSIVCD from those with genuine conduction delay induced by the conduction disorder. This finding is in line with a previous cardiac resynchronization therapy study, which investigated the influence of the definition of LBBB in patients with HF. The study results showed that the Strauss' definition was significantly better than other definitions of LBBB in predicting survival (Jastrzebski et al., 2018).

We found a strong independent association between NSIVCD and CV mortality even after adjustment for baseline cardiac comorbidities, and the association was strongest for non-specific $IVCD_{STRAUSS}$. Although less studied than LBBB and RBBB and probably under-diagnosed by clinicians, there are studies showing a strong correlation between NSIVCD and CV mortality. Regional myocardial scarring as a result of fibrosis, left ventricular hypertrophy, or previous MI has been considered as pathophysiological background factors for NSIVCD (Eschalier et al., 2015; Haataja et al., 2015). This conduction disorder alters left ventricular conduction, which results in a broad QRS complex not typical for RBBB or LBBB. In the retrospective Palo Alto Veterans Affairs Medical Center study ($n = 46,933$), every 10 ms increase in QRS duration without bundle branch block increased CV risk by 18% (Desai et al., 2006). In a

Finnish community-based CHD Study (n = 10,899) carried out between 1966 and 1972, NSIVCD was a predictor of all-cause and CV mortality with an increased risk of sudden arrhythmic cardiac death (Aro et al., 2011). In Women's Health Initiative study, NSIVCD was independently associated with increased CV mortality in women with known CV disease. In women without CV disease, NSIVCD was not a predictor of all-cause mortality and CV mortality was not reported (Zhang et al., 2012). The results from the current study emphasize NSIVCD as a marker of increased mortality especially in subjects with prevalent heart disease.

Although RBBB had a frequent association with CV comorbidities in the present study, no relation to adverse prognosis was found in the general population. However, in subjects with prevalent heart disease, RBBB was associated with higher CV but not with all-cause mortality. In the Copenhagen City Heart Study (n = 18,441; Bussink et al.., 2013), RBBB was associated with increased risk of all-cause and CV mortality in subjects free from previous MI or HF but the prevalence of stable CHD was not reported. In the Women's Health Initiative study (Zhang et al., 2012), RBBB was associated with CV mortality only in women with CV disease at baseline, and likewise was not associated with mortality in subjects without angina or dyspnea at baseline in the Primary Prevention Study (Eriksson et al., 2005).

The data regarding prognosis of incomplete bundle branch blocks in general population are scarce. ILBBB is thought to result from slowing of conduction in the left bundle branch, and an association with CHD and hypertensive heart disease was found in a study from the 1960s (Wassenburger, White, & Lindsay, 1963). In the present study, iLBBB was associated with previous MI and was related to mortality only in unadjusted Cox regression analysis. Conversely, iRBBB was not associated with mortality in absence of heart disease, similar to the results of the Copenhagen Heart Study (Bussink et al.., 2013) and to an older Chicago Western Electric Company Study (n = 1,960; Liao et al., 1986). However, in exploratory subgroups analyses, we found that among subjects with heart disease iRBBB associated with increased and all-cause mortality suggesting that iRBBB might not be a harmless finding. We found no prior prospective population studies regarding this matter. iRBBB has been associated with exercise-induced physiological left ventricular remodeling and right ventricular enlargement (Kim et al., 2011), right ventricular pressure overload (Digby et al., 2015), and degenerative heart disease of the elderly (Bussink et al.., 2013). Thus, iRBBB observed in early life may be of a different etiology than in the elderly (Nielsen et al., 2011).

In epidemiological studies, the association of LAFB and CV diseases has shown varied results. In patients with suspected CHD and no history of MI (n = 1,187; Biagini et al., 2005), LAFB was associated with increased CV mortality. In the Kailuan study (n = 101,510; Yiheng et al., 2016), no association between LAFB and mortality was found. In the present study, no relation to adverse prognosis was found although LAFB was related to multiple cardiac comorbidities. Some overlap between left axis deviation and LAFB is unavoidable, and isolated left axis deviation is a common, age-associated ECG finding not associated with adverse prognosis (Ostrander, 1971).

As in previous studies, LPFB was an infrequent IVCD in the present study. Anatomically, the left posterior fascicle is shorter and thicker than the left anterior fascicle. In addition, the posterior fascicle has double arterial blood supply (Elizari et al., 2007). LPFB is often encountered with RBBB (Godat & Gertsch, 1993) as a precursor of complete heart block (Boule et al., 2014; Elizari et al., 2007). Earlier studies associated LPFB with severe myocardial damage (Godat & Gertsch, 1993). However, the low number of subjects even in a large nationwide study makes it difficult to draw any firm conclusions about the clinical significance of this conduction disorder.

The R-R' pattern proved to be a benign ECG finding. In lead V1-V2, the presence of R > R' may be due to misplacement of the ECG electrodes in the 2nd intercostal place, especially when accompanied by a negative P wave in lead V1. In a previous study, the R-R' disappeared when the electrodes were properly positioned (Baranchuk et al., 2015). Another possible cause for this ECG manifestation is a normal variant due to delay in the activation of the basal part of the right ventricle (Baranchuk et al., 2015).

While the guidelines are less stringent in patients with conduction disorders other than LBBB, clinical evaluation and transthoracic echocardiography might be useful to rule out structural heart disease in subjects with NSIVCD. In isolated LBBB, the former is prudent (Kusumoto et al., 2018) as LBBB may not only indicate adverse prognosis but also have influence on the management of the heart disease. While bundle branch blocks may point to a greater degree of myocardial involvement and damage in subjects with prevalent heart disease, in some patients they may also indicate degeneration of the conduction system with no relation to impaired prognosis.

Several study limitations need to be pointed out. First of all, absence of imaging data is a study limitation typical of a population study. Furthermore, only one ECG for each subject was recorded. We also lack data related to possible changes in medication during follow-up. We think that the large study population representing a wide age range from both genders, well-defined baseline characteristics, and long follow-up gives strength to our study findings.

In conclusion, in a population study of individuals aged 30 or older with long-term follow-up, LBBB and NSIVCD were associated with CV mortality. The definition of LBBB has influence on outcome. In further subgroup analyses, NSIVCD, LBBB, iRBBB, and RBBB were associated with mortality only in subjects with known heart disease. Other intraventricular conduction disorders had no significant impact on prognosis. These differences in the prognostic significance of different IVCDs need to be taken into account in everyday clinical practice.

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CONFLICTS OF INTEREST

None.

ETHICAL APPROVAL

The study protocol of the Health 2000 survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Relation of intraventricular conduction delay to risk of new-onset heart failure and structural heart disease in the general population.

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Relation of intraventricular conduction delay to risk of new-onset heart failure and structural heart disease in the general population

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ABSTRACT

Background: Intraventricular conduction delays (IVCDs) are hallmarks of heart failure (HF) and structural heart disease (SHD) but their prognostic value for HF and SHD is unclear.
Methods: Relation of eight IVCDs and the incidence of first-time HF or SHD was studied in a nationally representative random sample of 6080 Finnish subjects aged ≥ 30 years (mean age 52.1, SD 14.5 years) who participated in the health examination including 12-lead ECG.
Results: During 16.5 years' follow up, half of the subjects with left bundle branch block (LBBB) and one third of the subjects with non-specific IVCD developed HF. After controlling for known clinical risk factors the hazard ratio (HR) for new-onset HF for LBBB was 3.29 (95% confidence interval 1.93–5.63, P < 0.001) and 3.53 for non-specific IVCD (1.65–7.55, P = 0.001). In corresponding analysis, LBBB predicted SHD with HR 2.60 (1.21–5.62, P = 0.015). Excluding subjects with history of heart disease, including coronary heart disease, did not have impact on results. Right bundle branch block and other IVCDs displayed no relation to endpoints.
Conclusion: LBBB and non-specific IVCD were associated with more than three-fold risk of new-onset HF. Furthermore, LBBB was associated with novel SHD. Their presence should alert clinician even in subjects free from any known heart disease.

1. Introduction

Intraventricular conduction delays (IVCDs) have been associated with impaired prognosis in patients with known cardiac disease. Left bundle branch block (LBBB), right bundle branch block (RBBB), and non-specific IVCD were associated with increased mortality especially in patients with myocardial infarction (MI) [1–3] and heart failure (HF) [4–7]. Mortality rates remain high in symptomatic patients with advanced HF and reduced ejection fraction in spite of improvements in medical therapy and effective utilization of cardiac resynchronization therapy. For timely initiation of therapy, subjects with high-risk of developing HF ought to be identified. Literature assessing the role of IVCDs as risk markers for the development of HF is scarce and has presented conflicting results, and has evaluated only selected bundle branch block categories [8–11].

IVCDs are frequent in patients with structural heart disease (SHD) [12], including valvular heart diseases and cardiomyopathies, but no prior prospective population studies have related IVCDs to novel SHD in subjects without known heart disease. Studies conducted in recent years have evaluated the role of LBBB in inducing left ventricular systolic decline [13,14], while RBBB should play no significant negative role in this aspect [15]. Non-specific IVCD has previously been associated with cardiovascular (CV) mortality [16] and sudden cardiac death [17,18], but the pro-

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gression to HF has not been extensively studied in patients without overt cardiac disease. Study data regarding the prognostic implications of fascicular blocks, incomplete bundle branch blocks and the R-R' pattern in either of the leads V1 or V2 to predict HF is practically non-existent.

The aim of this study was to explore the association between IVCDs and new-onset HF and SHD in an unbiased random sample of predominantly Caucasian general population during 16.5 years of total follow-up.

2. Methods

2.1. Study population

The Health 2000 is a major Finnish health examination survey. The survey was carried out in 2000–2001, and a representative stratified random cluster sample of the Finnish population was examined. The purpose of the survey was to provide an up-to-date epidemiological data of major public health problems in Finland, their causes and treatment. In brief, a representative stratified random cluster sample of the Finnish population was examined. The sampling included both largest cities and smaller regions and suburbs. For the population aged $\geq$ 80 years, the sampling probability was twice as high as among those <80 years. The implementation of the survey is described in detail elsewhere [19]. The Health 2000 sample comprised 8 028 individuals (3 637 men and 4 391 women) aged 30 or older, of whom 79% (6 354 individuals; 2 876 men and 3 478 women) participated in the health examination. The health examination was performed on each participant 1–6 weeks later at a local health center by centrally trained professional doctors and nurses. After a home interview a comprehensive health examination including questionnaires, measurements (e.g. blood pressure, resting electrocardiogram (ECG)) and physician's physical examination was performed. The National Care Register for Health Care and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data.

We excluded subjects with prevalent HF and SHD from the study (Fig. 1). Thus, the analysis was performed with 6080 subjects: 3298 women and 2 782 men (mean age 52.1, SD 14.5 years). The study protocol of the Health 2000 Survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants in the survey signed an informed consent both before the health interview and at the beginning of the health examination.

2.2. ECG analysis and registration

The main exposure variables were IVCDs - for their identification, both Minnesota codes and measurements based on the Magellan software program were used. Four of the conduction delays were classified according to the respective Minnesota classes: RBBB (code 7–2), incomplete RBBB (iRBBB) (code 7–3), the R-R' pattern in either of leads V1 and V2 with R' amplitude $\leq$ R (R-R′ pattern) (code 7–5), and incomplete LBBB (iLBBB) (code 7–6) [20]. LBBB was defined by the Strauss definition [21]. Nonspecific IVCD was defined as QRS duration $\geq$ 120 ms not meeting RBBB or LBBB criteria (Fig. 2). For left anterior fascicular block we used the following definition: frontal QRS axis between −30° and −90°, rS configuration in II, III, and aVF, and qR configuration in aVL, with a QRS duration less than 120 ms. Left posterior fascicular block was defined as frontal QRS axis >120°, lead I rS configuration, leads II, III, and aVF qR configuration, and no pathological Q waves in leads II, III, aVF. The accuracy of the Minnesota coding and IVCD classification was checked by manual ECG analysis by three of the authors (JR, PH, and KN), blinded to the clinical outcome of the subject.

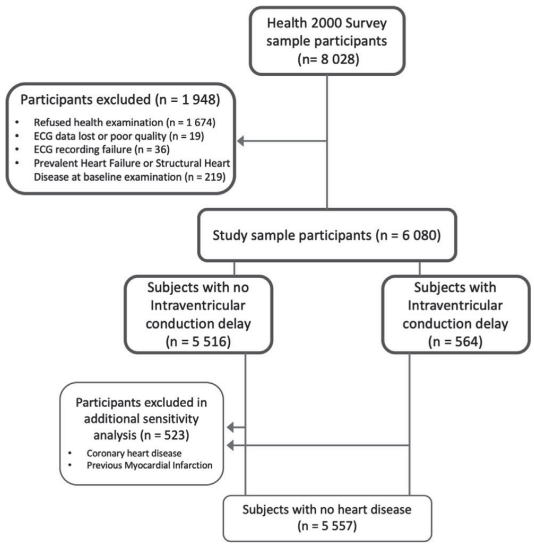

Fig. 1. Flow chart of the Health 2000 study population.

Standard 12-lead ECGs were recorded in the resting supine position by MAC 5000 recorders (Marquette Hellige, Freiburg, Germany and Milwaukee, WI, USA) and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige, Milwaukee, WI). All ECGs were read, and the computerized diagnoses and measurements corrected if needed, by a physician experienced with ECG before being stored in the database. ECG was recorded and printed using a paper speed of 50 mm/s. The maximal filter setting of the system (150 Hz) was used. The Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators who were blinded to the clinical data of the patient. ECGs were obtained successfully in 6 318 individuals (99%) who attended the health examination. Nineteen ECGs were rejected owing to data lost in further processes. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding scheme [22]. The electrical recordings were analyzed by means of Magellan software program (Marquette Electronics Inc., Milwaukee, WI, USA).

2.3. Classification of prevalent conditions and other measurements

Classification as coronary heart disease (CHD) required at least one of the following: diagnosis of MI and/or angina pectoris during the field health examination by a physician, large Q waves in the resting ECG, hospitalization for CHD (International Classification of Diseases [ICD]-8 or ICD-9 codes 410–414 or ICD-10 codes I20–I25), a history of coronary revascularization procedure, the right to drug reimbursements for CHD, or the use of nitroglycerine combined with an anticoagulant, acetyl salicylic acid, or beta-blocker. The Finnish Care Register for Health Care has been shown to be valid in identifying major CHD events [23].

Classification for MI required either a clinical diagnosis of old MI by the examining physician, large Q waves in the resting ECG, or a previous discharge diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21–I22). Old MI was defined as a positive history of the condition in the medical records or old MI on ECG, or typical

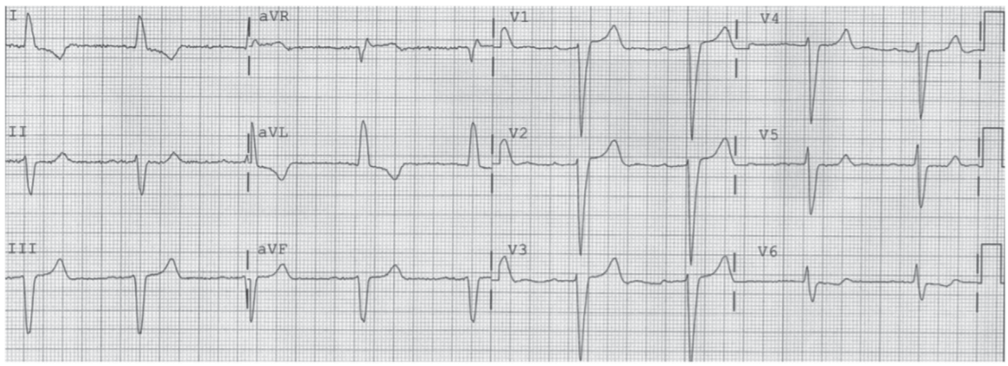

Fig. 2. The 12-lead ECG of a healthy subject with non-specific IVCD. The criteria for left bundle branch block are not fulfilled: QRS duration is 122 ms without notching or slurring in at least two contiguous leads [21]. The subject developed heart failure during the study follow-up.

self-reported history of MI treated in a hospital. Large Q waves indicating probable previous MI included Minnesota codes 1.1–1.3.

HF classification required a clinical diagnosis by the examining physician and either a previous discharge diagnosis of HF (ICD-8 code 4270, ICD-9 code 428, or ICD-10 code I50) or the right to drug reimbursements for HF. The classification for SHD required a previous diagnosis of SHD (ICD-9 codes 39, 425, 746, or ICD-10 codes I34–I37, I39, or I42). The classification for stroke required one or more discharge diagnoses of stroke (ICD-8 codes 430–431, 433–434, ICD-9 codes 430–434, or ICD-10 codes I60, I61, I63). Classification for peripheral arterial disease (PAD) required a clinical diagnosis by the examining physician or previous hospitalization for PAD.

The health examination included measurements of height, weight, body mass index (BMI), and waist circumference. Blood pressure (BP) was measured three times with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, Juningen, Germany) from the right arm. Hypertension was defined as a clinic average BP $\geq$ 140/90 mmHg or right to drug reimbursements for hypertension. Diabetes mellitus was defined as a serum glucose level of 7.0 mmol/L or greater or a history of the use of oral hypoglycemic agents or insulin therapy. Heart murmur was defined as a systolic or diastolic murmur heard at physician's physical examination. Smoking was defined as daily use of tobacco products. Laboratory tests included measurements for high-density lipoprotein cholesterol, total cholesterol, triglyceride, and serum glucose. Low-density lipoprotein cholesterol was calculated with the Friedewald formula.

2.4. Follow-up

From the baseline examination between 2000 and 2001, the participants were followed up for the main study endpoints until the end of 2015 (total follow-up time 16.5 years, median 15.9 years). Two study endpoints were used: new-onset HF and SHD. New-onset HF was defined as a hospitalization with the pre-described ICD-codes for HF from the Care Register for Health Care, new right to drug reimbursements for HF, or pre-described ICD-codes for HF as the primary underlying or immediate cause of death from the Causes of Death Register. New-onset SHD required a new diagnosis of SHD with the pre-described ICD-codes for SHD from the Care Register for Health Care, or pre-described ICD-codes for SHD as the primary underlying cause of death from the Causes of Death Register. Only the first event was included in the analyses. The follow-up information was gathered by linking the personal identity code from the Health 2000 Survey database to the Care Register for Health Care and the Causes of Death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens in Finland and nearly 100% abroad. Diagnoses are registered in these registers by the treating physicians with codes defined in ICD-10. The follow-up information was available for all subjects. The Finnish Care Register for Health Care has been shown to be valid in identifying HF diagnoses and can be reliably used for research purposes [24].

2.5. Statistical analyses

In the Health 2000 Survey, proportions were compared with the chi-square test or Fisher's exact test. Data were categorized into nine groups according to the presence and type of IVCD. The complex sampling design was taken into account by correcting for the oversampling of subjects over 80 years of age. Unadjusted survival to each endpoint was assessed using the Kaplan–Meier method comparing differences between the reference population and subjects with IVCDs at baseline. Adjusted Hazard ratios (HR) were calculated by univariate and multivariate proportional Cox regression model analysis. Multivariate analysis included the following parameters: age, sex, CHD, MI, hypertension, diabetes mellitus, smoking, body mass index and low-density lipoprotein cholesterol. Additional sensitivity analyses were performed excluding subjects with history of heart disease (CHD, previous MI, including Q waves in the resting ECG) and subjects with heart murmurs. All analyses were performed with the SPSS release 25.0 for Windows (IBM Corp, Armonk, NY). A P-value of less than 0.05 was considered to be statistically significant.

3. Results

The prevalence of IVCDs in the general population without HF or SHD was 9,3% (n = 564), with a rather infrequent prevalence of conduction blocks with broad (>120 ms) QRS (LBBB, RBBB or non-specific IVCD) of 2,2% (n = 136). The clinical characteristics of the study population are presented in Table 1. Subjects with LBBB, non-specific IVCD, RBBB and LAFB were older and more often had prevalent CHD, while LBBB and non-specific IVCD were associated with previous MI. Subjects with LAFB presented higher levels of low-density lipoprotein cholesterol. Heart murmurs were more often heard in subjects with RBBB, non-specific IVCD and LBBB.

Table 1
Clinical characteristics and morbidity of the study population according to presence of intraventricular conduction delay.

	No IVCD (n = 5516)	LBBB (n = 37)	RBBB (n = 61)	Non-specific IVCD (n = 38)	LAFB (n = 58)	LPFB (n = 8)	iLBBB (n = 61)	iRBBB (n = 59)	R-R' pattern (n = 242)
	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)	Mean/n (%)
Sex (male, %)	44.2	45.9	63.9	81.6	56.1	75.0	77.2	54.2	48.8
Age (years)	51.5 ± 14.2	70.4 ± 11.6*	68.0 ± 14.7*	57.9 ± 16.6*	64.0 ± 14.2*	38.8 ± 12.2*	52.6 ± 16.3	58.2 ± 14.8*	53.6 ± 14.7
Smoking (current)	1512 (27.6)	7 (18.9)	14 (23.0)	5 (13.2)*	8 (14.0)*	1 (12.5)	18 (31.6)	12 (20.3)	69 (28.5)
LDL cholesterol (mmol/L)	3.7 ± 1.1	3.9 ± 1.1	3.8 ± 1.0	3.6 ± 0.8	4.3 ± 1.4*	3.6 ± 1.0	3.8 ± 0.9	3.8 ± 1.2	3.8 ± 1.1
BMI (kg/m^2)	26.9 ± 4.6	27.4 ± 4.2	26.9 ± 3.8	27.3 ± 3.9	26.7 ± 4.8	23.1 ± 1.6*	28.9 ± 3.7*	26.1 ± 4.1	26.0 ± 4.5*
QRS duration (ms)	90.6 ± 11.7	154.8 ± 16.7*	136.8 ± 11.5*	125.3 ± 7.8*	94.9 ± 10.7*	103.0 ± 8.2*	107.3 ± 5.6*	94.8 ± 10.7*	91.1 ± 10.6*
Hypertension	2525 (46.2)	30 (81.1)*	40 (65.6)*	28 (73.7)*	42 (73.7)*	1 (12.5)	32 (56.1)	31 (52.5)*	112 (46.3)
Diabetes mellitus	282 (5.1)	5 (13.5)*	4 (6.6)	3 (7.9)	4 (7.0)	0	3 (5.3)	5 (8.5)	7 (2.9)
Heart murmur	466 (8.5)	7 (18.9)*	13 (21.3)*	8 (21.1)*	7 (12.3)	0	7 (12.3)	5 (8.5)	19 (7.9)
Coronary heart disease	431 (7.9)	17 (45.9)*	17 (27.9)*	11 (28.9)*	10 (17.5)*	0	4 (7.0)	9 (15.3)	17 (7.0)
Myocardial infarction	149 (2.7)	8 (21.6)*	4 (6.6)	10 (26.3)*	3 (5.3)	0	2 (3.5)	3 (5.1)	8 (3.3)
Stroke	179 (3.3)	3 (8.1)	4 (6.6)	5 (13.2)*	4 (7.0)	0	0	4 (6.8)	12 (5.0)
Peripheral artery disease	71 (1.3)	2 (5.4)	2 (3.3)	5 (13.2)*	2 (3.5)	0	1 (1.8)	1 (1.7)	4 (1.7)
Medication									
ACI/ARB	396 (7.2)	8 (21.6)*	4 (6.6)	7 (18.4)*	4 (7.0)	0	4 (7.0)	8 (13.6)	16 (6.6)
Beta adrenergic blockers	704 (12.8)	16 (43.2)*	15 (24.6)*	12 (31.6)*	9 (15.8)	1 (12.5)	4 (7.0)	14 (23.7)*	35 (14.5)
Calcium channel blockers	287 (5.2)	4 (10.8)	8 (13.1)*	8 (21.1)*	4 (7.0)	0	0	4 (6.8)	18 (7.4)
Antithrombotics	421 (7.7)	8 (21.6)*	13 (21.3)*	11 (28.9)*	11 (19.3)*	0	7 (12.3)	12 (20.3)*	22 (9.1)
Diuretics	302 (5.5)	5 (13.5)	9 (14.8)*	7 (18.4)*	4 (7.0)	0	6 (10.5)	5 (8.5)	12 (5.0)
Statin	318 (343)	4 (10.8)	4 (6.6)	6 (15.8)*	2 (3.5)	0	3 (5.3)	5 (8.5)	11 (4.5)
Study primary enpoints									
Heart failure	347 (6.3)	18 (48.6)*	14 (23.0)*	12 (31.6)*	10 (17.5)*	0	7 (12.3)	8 (13.6)	24 (9.9)
Structural heart disease	241 (4.4)	8 (21.6)*	6 (9.8)	2 (5.3)	7 (12.3)*	0	5 (8.8)	3 (5.1)	13 (5.4)

ACI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist; BMI = body mass index; iLBBB = incomplete left bundle branch block; iRBBB = incomplete right bundle branch block; IVCD = intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LDL = low density lipoprotein; LPFB = left posterior fascicular block; RBBB = right bundle branch block. *P < 0.05

3.1. Outcome

During 16.5 years' follow up, 440 subjects developed new-onset HF and 285 subjects had a diagnosis of SHD. Table 1 also shows the rate of new HF and SHD during the follow up within the different IVCD categories. Subjects with LBBB, non-specific IVCD, RBBB, and LAFB had the highest rates of new-onset HF, while for SHD, the highest rates were found in the LBBB and LAFB categories.

In the age- and sex-adjusted Cox regression analysis (Table 2), HR for new-onset HF for LBBB was 3.61 (95% confidence interval [CI] 2.14–6.08, P < 0.001), and for non-specific IVCD 4.05 (95% CI 2.00–8.20, P < 0.001). In the multivariate adjusted Cox model, HR for new-onset HF for LBBB was 3.29 (95% CI 1.93–5.63, P < 0.001), and for non-specific IVCD 3.53 (95% CI 1.65–7.55, P = 0.001). RBBB and the other conduction blocks were not associated with the incidence of HF after adjustments for age and sex.

In the age- and sex-adjusted Cox regression analysis, the HR for SHD in subjects with LBBB was 3.18 (95% CI 1.56–6.47, P = 0.001). The corresponding HR in the multivariate adjusted Cox model was 2.60 (95% CI 1.21–5.62, P = 0.015). Non-specific IVCD and other conduction blocks were not associated with SHD during follow up either in the age- and sex-adjusted or the multivariate adjusted model.

In the Cox regression analysis of subjects (remaining subpopulation n = 5 557) with no history of heart disease, after adjustment for age and sex, the HR for new-onset HF in the subjects with LBBB and non-specific IVCD was 3.58 (95% CI 1.59–8.07, P = 0.002) and 5.14 (95% CI 2.26–11.66, P < 0.001), respectively. In corresponding analysis, HR for SHD for LBBB was 4.65 (95% CI 1.09–11.34, P = 0.001). When the subjects with heart murmurs were removed from analysis (n = 5 097), the HR for new-onset HF was 4.82 (95% CI 1.98–11.72, P = 0.001) for LBBB and 3.63 (95% CI 1.50–11.47,

Table 2
Adjusted Cox proportional hazard analysis for study endpoints according to intraventricular conduction delay.

Variable	New-onset heart failure			Structural heart disease		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age- and sex-adjusted						
LBBB (n = 37)	3.61	2.14–6.08	<0.001	3.18	1.56–6.47	0.001
RBBB (n = 61)	1.12	0.61–2.05	0.717	1.17	0.52–2.64	0.715
Non-specific IVCD (n = 38)	4.05	2.00–8.20	<0.001	1.10	0.27–4.44	0.892
LAFB (n = 58)	1.13	0.93–2.19	0.728	1.73	0.82–3.69	0.153
LPFB (n = 8)	no events			no events		
iLBBB (n = 61)	1.82	0.81–4.08	0.148	2.05	0.91–4.62	0.083
iRBBB (n = 59)	0.44	0.11–1.75	0.242	0.97	0.31–3.02	0.953
R-R' pattern (n = 242)	1.38	0.89–2.15	0.153	1.07	0.61–1.86	0.820
Multivariate[a]-adjusted						
LBBB	3.29	1.93–5.63	<0.001	2.60	1.21–5.62	0.015
Non-specific IVCD	3.53	1.65–7.55	0.001			

CI = confidence interval; iLBBB = incomplete LBBB; iRBBB = incomplete RBBB; IVCD = intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; RBBB = right bundle branch block. [a]Adjusted for age, sex, coronary heart disease, myocardial infarction, hypertension, diabetes mellitus, smoking, body mass index and low-density lipoprotein cholesterol.

P = 0.028) for non-specific IVCD, respectively. Regarding SHD, the HR in subjects with LBBB was 5.90 (95% CI 2.17–16.03, P = 0.001).

4. Discussion

Our study showed clinically important prognostic differences between the categories of IVCDs. We showed that both non-specific IVCD and LBBB are associated with new-onset HF, and LBBB is associated with novel SHD during long-term follow-up in a nationally representative population cohort. During the follow-up, half of the subjects with LBBB and one third of the subjects with non-specific IVCD developed HF. Novel SHD was found in one fifth of the subjects with LBBB. While RBBB and LAFB displayed higher rates of new-onset HF and SHD, neither of them alongside other conduction blocks were associated with novel HF or SHD after adjustments for age and sex.

A few previous prospective studies have addressed the relation of bundle branch blocks and HF. In a study of men born in 1913[25] (n = 855), a diagnosis of HF during follow-up was significantly more common among those with bundle branch block. In the Framingham Heart Study (n = 1759) [26], participants with LBBB (n = 26) but not those with RBBB (n = 59) were more likely to develop HF than those with a QRS duration < 100 ms. Similarly, in the Copenhagen City Heart Study (n = 18 441) [15], RBBB (n = 166) was not associated with increased risk of HF. In the Women's Health Initiative Study (n = 65 975) [10], LBBB (n = 680) and the combination of RBBB and LAFB (n = 139), but not isolated RBBB (n = 740), were predictors of incident HF. The current study corroborates previous study findings that RBBB is not associated with new-onset HF. In addition, our study results add information about the association of this conduction disorder and novel SHD - subjects with RBBB have no excess risk of developing SHD during long-term follow-up. No previous prospective population studies have investigated the possible association between IVCDs and SHD.

Similar to the results the Framingham Heart and Women's Health Initiative Studies, a 40-year follow up of 17 361 subjects in Hiroshima and Nagasaki [27], showed that LBBB (n = 110) was associated with mortality from HF. In the Primary Prevention Study in Gothenburg (n = 7 392) [9], LBBB (n = 46), but not RBBB (n = 70), was associated with increased risk of CHD death and HF in men without angina or dyspnea at baseline. The risk for developing HF was almost fourfold in men with LBBB, close to one observed in the present study.

The presence of LBBB in previous longitudinal studies was also significantly related to underlying cardiac comorbidities also linked to risk of HF. In the present study were able to exclude subjects with either previously known or symptomatic HF and excluding subjects with apparent heart disease at the baseline health examination did not have any significant impact on the results. However, the possibility of underlying silent cardiac conditions, such as reduced left ventricular function without symptomatic heart failure, cannot be excluded. Nevertheless, in a previous retrospective study of patients with LBBB (n = 94) and preserved ejection fraction [13], functional decline measured by change of left ventricular ejection fraction in transthoracic echocardiogram was found in over one third of the patients. Our results are similar demonstrating that approximately half of all subjects with LBBB but without symptomatic prevalent HF at baseline develop symptomatic HF over a long period of time.

One of the most likely causes of left ventricular functional decline in left bundle branch block is the associated mechanical dyssynchrony [14]. This is supported by the fact that biventricular pacing, which corrects dyssynchrony, is associated with a reverse in the LV mechanical decline as well as with better outcomes in patients with symptomatic HF and LBBB [14,28,29]. In an animal model [30], LBBB induced unfavorable ventricular dilation, remodeling and asymmetric hypertrophy in normal hearts. In addition, LBBB induces and aggravates mitral regurgitation by several mechanisms, which prevent normal coaptation of the valve leaflets [31]. These previously referred studies and the results of the current study strongly suggest LBBB alone has a causal role in the development of HF.

Past epidemiological data from 1950s to 1970s [32,33] and clinical experience has shown that isolated LBBB is not necessarily hazardous in younger population as a result of possible age interactions modulating the association between LBBB and novel HF, as younger hearts be capable to compensate the potential loss of ventricular function. This was shown in a large retrospective cohort study of primary care patients referred for ECG [34], where the risk chart depicting 10-year absolute risk of HF revealed the risk significantly increasing with age in subjects with LBBB. Unfortunately, due to limited number of subjects with LBBB in our study population, we are unable to present reliable estimates of this statement.

Previous research on the prognosis of non-specific IVCD has mainly focused on patients with prevalent HF [4,5,35], but the progression to novel HF has not been extensively studied. In contrast to LBBB, subjects with non-specific IVCD show less, but more heterogenous, dyssynchrony [36] and considerable variation in the location of the latest activated site of the left ventricle [37]. In the current study, subjects with non-specific IVCD carried the highest risk of developing HF. In the Women's Health Initiative Study [10], after excluding participants with HF (self-reported), non-specific IVCD (n = 117) was a predictor of incident HF in women. In the Framingham Heart Study population [26], after excluding individuals with prevalent HF or MI, non-specific IVCD (n = 28) was associated with a two-fold risk of HF in the subjects with this conduction disorder in the baseline (n = 1759) ECG in 1949. These findings support the results of the current study.

In the Cardiovascular Health Study (n = 1664) [11], which comprised individuals aged 65 or older, LAFB (n = 39) predicted HF in the absence of overt CV disease. The findings are opposite to the findings from our study, which displayed no relation between LAFB and HF after adjustments for age and sex. While the differences in studied populations might explain the divergence of the result, LAFB is generally considered as a benign ECG finding. Study data on the relation between LPFB and HF is scarce, as LPFB is an extremely rare finding both in the general population and in specific patient groups. As an entity, LPFB may occur in infiltrative cardiomyopathies [38], and LPFB with or without RBBB may be found in cases with Chagas disease [39], which is an important cause of cardiomyopathy in Latin America. No increased risk of HF or SHD was found in subjects with LPFB in this study but the low number of subjects prohibit any definitive conclusions to be drawn.

Incomplete bundle branch blocks and the R-R' pattern were not associated with increased risk of HF or SHD in the present study. The result are is in line with the Copenhagen City Heart Study [15], which showed no relation between iRBBB (n = 624) and HF. On the contrary, the prognostic implications of iLBBB and the R-R' pattern is poorly investigated, and therefore remain largely unknown. Our study results indicate that iLBBB and the R-R' pattern are neither precursors of HF nor SHD.

Several study limitations need to be pointed out. First of all, absence of imaging data is a study limitation typical of a population study, yet the purpose of this study was to evaluate the prognostic implications of IVCDs in the general population using the same information that is normally available in general practice. We also lack data related to possible changes in medication during

follow-up. We think that the large study population representing a wide age range from both genders, well-defined baseline characteristics, and long follow-up gives strength to our study findings.

5. Conclusions

In a population study of individuals aged 30 or older with long-term follow-up, LBBB and non-specific IVCD, independently of several baseline variables, were associated with a more than three-fold risk of new-onset HF. Furthermore, LBBB was associated with novel SHD. The presence of these ECG abnormalities should alert physicians for careful cardiac evaluation even in absence of cardiovascular symptoms. Future clinical studies should focus on whether clinical or imaging follow-up, such as a routine echocardiographic control, is prudent and cost-effective for early prevention and identification of HF in these patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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MANUSCRIPT III

Prevalence and long-term prognostic implications of prolonged QRS duration associated with left ventricular hypertrophy in the general population

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