The electrocardiogram (ECG) has been a very valuable risk-selection tool in both clinical and insurance medicine for many years. Indeed, the ability to correctly interpret rest and exercise ECGs is a key skill of the modern life insurance company medical director. Long-term clinical, population-based epidemiologic and insurance industry studies have identified specific ECG abnormalities that are predictive of increased mortality risk. The following hypothetical case illustrates a recently recognized ECG abnormality predictive of high risk of sudden unexpected death.

CASE PRESENTATION

Suppose you are asked to consider an application of a 34-year-old male who is applying for $500,000 of whole life insurance. The applicant was born in Thailand and lived there until age 22, when he immigrated to the United States to do graduate work in biochemistry. After he obtained his PhD, he was recruited by a large pharmaceutical company where he continues to be employed as a research biochemist. He is married and has 2 sons, age 4 and 6.

His past health has been normal and he currently has no medical problems. His father, age 42, and a paternal uncle, age 45, died suddenly and unexpectedly in their sleep. His family history is otherwise normal.

His examination is normal, including a BP of 125/80. Routine lab work is normal with no evidence of diabetes or hyperlipidemia. His ECG resembles the one shown in Figure 1. Would you have any concerns about the future mortality of this applicant?

DISCUSSION

In 1992, Brugada and Brugada described 8 patients with a history of aborted sudden
death and a distinct ECG pattern, consisting of right bundle branch block (RBBB) with ST-segment elevation in the right precordial leads (V₁, V₂, and V₃) and normal QTc interval, in the absence of any structural heart disease. In 4 of the reported patients, a family history was suspected. Since the original description, the entity has been increasingly recognized and has become the subject of increasing attention and some controversy.

The mechanism of sudden death in the Brugada syndrome is related to polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF). The absence of structural heart disease implies that the arrhythmogenic substrate is related to an electrophysiological derangement. For this reason, the Brugada syndrome is considered to be a form of primary electrical heart disease similar to the long-QT syndrome.

The ECG component of the Brugada syndrome is interesting and usually suggests the diagnosis. The right precordial lead (V₁–V₃) QRS pattern resembles that seen in the RBBB, although in many cases, the typical widened S wave in the left lateral leads is absent, suggesting that this is not a true RBBB. The QRS complex ends with a positive deflection (J wave) followed by an elevated down-sloping ST segment, and a negative T wave with a
normal QTc interval. The combination of the RBBB and the ST-segment pattern is sometimes referred to as the Brugada sign.

Usually, the ST-segment elevation has a convex curved or coved form (felt by some observers to have stronger arrhythmogenic potential) but changes into a saddle-shape; or complete normalization in up to 30% of cases.² The prevalence of the typical coved ST-segment pattern in the general population has been estimated to be 0.1% and the saddle-shape to be 6%.⁵

A definite Brugada sign is a specific marker of high risk. However, less-definite ECG abnormalities (sometimes referred to as “pseudo-Brugada” signs) such as the saddle-shaped ST segment without the coved pattern appear to have little diagnostic or prognostic significance in short-term follow-up studies.⁶

Loss of the ECG signature of this syndrome may lead to an underestimation of the prevalence and underdiagnosis of the disease. Individuals who have the concealed or transient form of the syndrome appear to have the same risk of potentially lethal arrhythmias as do those with overt disease. Sodium channel blockade using agents such as flecainide, procainamide, and ajmaline can unmask the typical Brugada ECG pattern in those in whom doubt about the diagnosis remains. These drugs are being used as a diagnostic challenge to patients who present with idiopathic VF and a normal ECG, and in screening asymptomatic family members of affected patients who have a normal ECG (Figure 2).⁷ However, the assumption that there is a 100% correlation between phenotype (the typical ECG, persistent, intermittent, or unmasked by drugs) and genotype has been challenged by recent reports of negative drug challenge tests in patients known to have mutations of the sodium channel genes discussed below. The risk of phenotypically negative, asymptomatic gene carriers is unknown at this time.⁸

The ST-segment elevation in the right precordial leads is observed in a variety of clinical settings and by itself is not unique or highly specific for the Brugada syndrome.³ Early repolarization syndrome (ERS) is different from the Brugada syndrome in that it is generally not associated with arrhythmias. It can be differentiated from the ST-segment elevation in the Brugada syndrome by its location and pattern. The elevated ST segment in ERS is usually localized to V₂–V₄ and has an upward concavity with positive T wave polarity accompanied by a notched J point.

Analysis of the reported cases of Brugada syndrome has revealed a number of additional interesting observations.³–⁵ The majority of cases have been male. The mean age at first arrhythmic event (VT or VF) has ranged between 22 and 65 years, most commonly occurring in the fourth decade. The recurrence rate of new arrhythmic events is as high as 40%.

A strong link has been identified between the Brugada syndrome and the sudden and unexpected death syndrome seen in Southeast Asian men.¹⁰¹,¹⁰ Nocturnal death in previously healthy young men (Pokkuri disease) is a well-recognized entity in Japan. Similar “sleep-death” syndromes have been described in the Philippines (Bangungut or “arise and moan”) and Thailand (Lai-Tai or “died during sleep”). A high percentage of individuals with these sleep-death syndromes have a resting ECG indistinguishable from that seen in the Brugada syndrome.

Brugada’s syndrome is inherited as an autosomal dominant trait in about 30% of families. In 20% of the cases, no clear pattern of inheritance can be defined. The remaining 50% of the cases are sporadic.¹¹

The suspected inherited occurrence of the entity suggests the possible involvement of defective ion channels (“ion channelopathy”⁴ as in the long-QT syndrome. Screening of some families with the Brugada phenotype has revealed distinct mutations in the gene (SCN5A) that encodes the pore-forming α-subunit of the cardiac sodium channel.¹⁰,¹²

Most symptomatic Brugada patients have polymorphic VT or VF inducible at electrophysiologic study. Pharmacological antiarrhythmic treatment including amiodarone has been disappointing and some drugs po-
tentially increase the risk. Treatment with an implantable cardioverter-defibrillator (ICD) is the only effective therapy to prevent sudden death in symptomatic individuals. More difficult to manage and assess risk in, are those asymptomatic individuals with the typical ECG pattern, either spontaneously or after administration of sodium channel blocker. Although current data do not allow precise risk stratification of this group, several authors recommend ICD implantation in those with inducible VT/VF or a malignant family history.

IMPLICATIONS FOR UNDERWRITING

An applicant such as the one illustrated in our hypothetical case has several of the features indicative of high risk. Lack of symptoms does not diminish the risk. The prevalence of such applicants in an insurance population will be low.

Applicants with a history of syncope or family history of sudden death accompanied by an ECG containing less typical (“pseudo-Brugada”) findings will occur more frequently and challenge the medical director. Depending on the findings, further evaluation by a cardiologist may be required before making a decision to offer life insurance.

In conclusion, Brugada and Brugada2 have identified a distinct subgroup of sudden unexpected death candidates who may be identified by a commonly used screening test in insurance medicine, the ECG. At present there are many gaps in our knowledge about this condition, and it is important to recognize that some of the information that we have regarding screening, natural history, and mortality undoubtedly reflects the referral bias that occurs when a new condition is first described.

REFERENCES