Epidemiology and clinical aspects of sudden cardiac death in the young
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Catecholaminergic polymorphic ventricular tachycardia: from bench to bedside

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SUMMARY

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by the occurrence of adrenergic mediated polymorphic ventricular tachyarrhythmias.

Mutations in the cardiac ryanodine receptor (RYR2) underlie the majority of CPVT cases and are inherited in an autosomal dominant fashion.

Mutations in RYR2 and other genes involved in CPVT cause spontaneous diastolic calcium release from the sarcoplasmic reticulum, which eventually lead to triggered arrhythmias.

The gold standard for the diagnosis of CPVT is exercise testing, although Holter monitoring or adrenaline infusion may be indicated in individual cases.

β-blockers are the mainstay of drug therapy in CPVT, while flecainide and left cardiac sympathetic denervation can be added or performed in patients with significant ventricular arrhythmias or arrhythmic events on β-blocker treatment. Implantable cardioverter-defibrillator implantation in CPVT patients should be restricted because of the potential proarrhythmic effect.
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome or so-called ‘channelopathy’. CPVT is characterized by the occurrence of adrenergic mediated polymorphic ventricular tachyarrhythmias (Figure 1).¹ The prevalence of CPVT in the general population is unknown, but has been estimated at 1 in 10 000. Although a rare disease, recognition of CPVT is important because of its high mortality rate of up to 50% in severely affected untreated individuals up till the age of 20.¹ Accordingly, CPVT probably plays a significant role in autopsy-negative sudden unexplained death of young individuals,² and sudden infant death syndrome (i.e., sudden death of an infant under 1 year of age that remains unexplained after a death scene and medicolegal investigation including a complete autopsy and clinical history review).³

For the last 15 years, significant progress has been made in our understanding of genetic, pathophysiological and clinical aspects of CPVT. The aim of this paper is to offer a perspective on molecular genetics, disease pathogenesis, clinical and genetic diagnosis, therapeutic strategies, and prognosis in CPVT.

Figure 1. Polymorphic ventricular arrhythmias during a treadmill exercise test of a 68-year-old female RYR2 mutation associated catecholaminergic polymorphic ventricular tachycardia patient. (A) Resting ECG. (B–D) ECGs during exercise, showing an increasing polymorphic ventricular arrhythmia burden, starting with isolated and bigeminal ventricular premature beats, and ending with bidirectional and polymorphic couplets and non-sustained ventricular tachycardia.
GENETIC BACKGROUND
The familial nature of CPVT was recognized in 1960 by Berg, who described three sisters with Adams-Stokes syndrome and polymorphic ventricular arrhythmias (VA) in the absence of organic heart disease, one of whom died suddenly. This hypothesis became even more probable when Coumel and coworkers from Paris published their two reports in 1978 and 1995, which provided the basis for acknowledging CPVT as a distinct disease entity.

In 1999 Swan et al linked the CPVT phenotype to a disease locus on chromosome 1q42-q43 and suggested the autosomal dominant inheritance pattern of this CPVT form. The disease-causing gene residing on this locus, the cardiac ryanodine receptor gene ($\text{RYR2}$) was first reported in two separate papers by Priori et al and Laitinen et al in 2001. $\text{RYR2}$ is a critical component of calcium homeostasis and associated excitation-contraction coupling in the cardiac myocyte. Mutations in $\text{RYR2}$ have also been identified in patients with fibrofatty myocardial replacement in the right ventricle, similar to arrhythmogenic cardiomyopathy, and intracellular calcium deposits, but this association is nowadays questioned. In addition, members from two separate families with a large genomic deletion in $\text{RYR2}$, involving exon 3, showed sinoatrial and atrioventricular node dysfunction, atrial fibrillation and atrial standstill in addition to the classic CPVT phenotype.

Also in 2001, Lahat et al reported a malignant autosomal recessive inherited form of CPVT in seven related Bedouin families. The disease locus was mapped to chromosome 1p13-21, and shortly thereafter a missense mutation was identified in the gene encoding cardiac calsequestrin ($\text{CASQ2}$). $\text{CASQ2}$ is located within the sarcoplasmic reticulum (SR) and also plays a pivotal role in calcium homeostasis.

A third CPVT form, inherited as an autosomal recessive trait, was mapped to chromosome 7p14-p22 by Bhuiyan et al in a report including four children from an inbred Arabic family. The disease-causing gene has remained elusive to date. Very recently mutations in triadin ($\text{TRDN}$), a transmembrane SR protein and another component of calcium homeostasis, were found to underlie an autosomal recessive form of CPVT in two families. Importantly, skeletal muscle weakness appeared to be another feature of this CPVT form. Finally, mutations in the gene encoding the potassium inwardly-rectifying channel Kir2.1 ($\text{KCNJ2}$), which generally are associated with Andersen-Tawil syndrome, sometimes underlie a CPVT phenocopy (see Differential diagnosis).

DISEASE PATHOPHYSIOLOGY
Cardiac excitation-contraction coupling is initiated by calcium influx through the L-type calcium channels in the sarcolemma during the plateau phase of the action potential (Figure 2), which triggers calcium release from the SR - the main intracellular calcium storage of the cardiac myocyte - through $\text{RYR2}$. This mechanism is termed calcium-induced calcium release. The released calcium binds to troponin C and eventually results in myocardial contraction. This is followed by the relaxation phase when SR calcium release is terminated. The released calcium is mainly taken up by the SR calcium-ATPase pump into the SR, or extruded from the cell by the sodium/calcium exchanger (NCX).

Mutations in $\text{RYR2}$, $\text{CASQ2}$, and probably also $\text{TRDN}$ eventually cause spontaneous diastolic calcium release from the SR. The subsequent increased cytosolic calcium concentration
activates the electrogenic NCX, leading to a transient inward current, which eventually produces delayed afterdepolarizations that may lead to triggered arrhythmias. The spontaneous diastolic calcium release is especially enhanced under conditions of β-adrenergic stimulation. It has been suggested that in CPVT this mechanism principally originates in the His-Purkinje system.22-24 The exciting new development of generating induced pluripotent stem (iPS) cells from patients with genetic diseases to explore the pathophysiology of human diseases in vitro has also been
applied to RYR2 mutation-related CPVT. In both models the results were in accordance with the previously described pathophysiology.

At the molecular level two mechanisms by which RYR2 mutations lead to aberrant diastolic Ca\(^{2+}\) release have been hypothesized: a reduced binding affinity of the channel-stabilizing protein calstabin 2 (FKBP12.6), and destabilisation of the closed state of the channel by mediation of defective interdomain interaction. The S406L iPS model indicated that a defective interdomain interaction is the most probable pathophysiological mechanism of this mutation.

Mutations in CASQ2 probably cause CPVT by several independent mechanisms. First, loss of CASQ2 may lead to a reduced direct inhibitory effect on RYR2. Second, mutated CASQ2 can result in a loss of Ca buffering, because CASQ2 is the main calcium buffering protein of the SR. Finally, CASQ loss may lead to remodelling of SR structure and proteins, particularly a reduction of the CASQ2 binding proteins triadin and junctin. TRDN mutations could cause CPVT by an impaired FKBP12.6-RYR2 interaction or a reduction of CASQ2. Interestingly, RYR2 dysfunction, along the same lines, is also believed to underlie fundamentally the increased arrhythmogenic susceptibility of patients with severe heart failure. This provides the opportunity to test potential antiarrhythmic drugs for heart failure in experimental models of CPVT. In addition, recent evidence confirmed the hypothesis that at the atrial level a similar mechanism underlies chronic atrial fibrillation.

**DIAGNOSIS**

**Clinical diagnosis**

**Clinical approach**

Classic CPVT patients are normally developed children aged 3 to 16 years presenting with syncope, aborted cardiac arrest (ACA) or sudden cardiac death (SCD) in circumstances of physical or emotional stress, including swimming. Children may initially be diagnosed with epilepsy, also because CPVT-related syncope may be accompanied by convulsive movements and urinary or fecal incontinence. CPVT may be diagnosed during follow-up when antiepileptic drugs are found to be ineffective. Another important feature of history taking may be a family history of syncope, ACA, SCD, or ‘epilepsy’ under similar conditions. Non-classic cases include adults in whom CPVT is diagnosed after becoming symptomatic for the first time in adulthood, or after an accidental finding of VA during cardiovascular screening that includes exercise testing. In addition, RYR2 mutations have been identified in victims of sudden infant death syndrome, suggesting the existence of extremely malignant forms of CPVT. A 12-lead ECG does not show any relevant abnormalities; in particular, there is no heart rate-corrected QT interval (QTC) prolongation. CPVT patients may be bradycardic, and this is thought to be more pronounced in males and in phenotypically affected RYR2 mutation-carriers as compared to genotype-positive, phenotype-negative patients. Cardiac imaging is usually unremarkable, and the absence of structural abnormalities is often considered a perquisite for the clinical diagnosis of CPVT. However, rare cases on a more complex phenotype in RYR2 mutation-carriers have been reported (see Genetic background). The gold standard for the diagnosis of CPVT is exercise testing by use of a treadmill or a bicycle ergometer. Indeed, a recent survey among 44 large European centers showed that 82% of
responders consider exercise testing of great value in asymptomatic patients suspected of CPVT. Typically, the heart rate threshold of the first isolated ventricular premature beat (VPB) is accurately reproducible in an individual patient by repeated exercise testing, and is usually 110 to 130 beats per minute. VPBs have a coupling interval of approximately 400 ms. Left bundle branch inferior axis and right bundle branch block superior axis morphologies are predominant. With increasing exercise duration and heart rate increase, the number of monomorphic isolated VPBs increases to bigeminal VPBs. Finally, mono- or polymorphic couplets or non-sustained ventricular tachycardia (NSVT) can be observed. Sometimes bidirectional ventricular tachycardia (VT) can be observed: VA with a beat-to-beat alternating QRS axis. Bidirectional VT is considered a hallmark of CPVT, but its sensitivity is low, and it is also associated with other conditions (see Differential diagnosis). In very rare cases, polymorphic sustained VT or ventricular fibrillation can be triggered by exercise testing. Some authors have reported the occurrence of supraventricular tachyarrhythmias during exercise testing, but in our experience this is rare. The test should be stopped when the patient experiences arrhythmic symptoms and/or the duration of NSVTs increases significantly. Importantly, in our experience with over 100 drug-naïve CPVT patients exercise testing under well-controlled conditions can be performed safely.

Holter monitoring can be performed in young children or other patients who are unable to perform an adequate exercise test, in patients suffering ACA, in patients suspected for emotion-related rather than exercise-related VA, in patients who report possible arrhythmia-related symptoms but have an unremarkable exercise test, or to assess the presence of brady- and/or supraventricular arrhythmias. However, the sensitivity of Holter monitoring to detect VAs in CPVT patients is thought to be lower than exercise testing. Some authors propagate the use of epinephrine infusion, which usually is initiated at a dose of 0.05 μg per kg per minute and then titrated at 5-minute intervals to a maximum dose of 0.2 μg per kg per minute. Provocation of VA in CPVT patients who did not have any VA on Holter monitoring or exercise testing, have been reported. In contrast, a recent study in 36 CPVT patients and 45 unaffected relatives concluded that epinephrine infusion has low sensitivity as compared to exercise testing. In this study epinephrine doses were accelerated to 0.4 μg per kg per minute, but the mean maximum heart rate was achieved after infusion of 0.2 μg per kg per minute and thereafter gradually declined. Maximum heart rate achieved upon epinephrine challenge was notably lower as compared to exercise testing. Among 25 CPVT patients with a positive exercise test, only seven had a positive adrenaline test (sensitivity of 28%). The specificity of epinephrine infusion in the entire study population was 98%.

During electrophysiology studies VA usually cannot be triggered other than by adrenergic stimulation. However, sinus node dysfunction may be identified and supraventricular tachyarrhythmias may be induced by burst atrial pacing. In addition, a recent paper reported on prominent postpacing changes of the QT interval in mutation-carriers from a family with the M4109R RYR2 mutation. Altogether, exercise testing is the diagnostic test of first choice, while cardiac imaging in indicated in the diagnostic work-up of index patients. The use of other tests may be tailored towards specific patients. A definite clinical diagnosis of CPVT can be made in patients with exercise- or emotion-induced bidirectional or polymorphic VT in the absence of structural heart disease and QTc interval prolongation. Possible CPVT patients have exercise-induced ventricular ectopy, not being polymorphic VT, in the absence of an alternative diagnosis.
First-degree relatives of mutation-negative CPVT index patients are advised to undergo cardiologic evaluation including exercise testing at least once. While evidence-based advice on the best follow-up strategy of these relatives is unavailable, we usually repeat exercise testing on a yearly basis in children and young adults, and dismiss middle-aged and older adults when the initial cardiologic evaluation is unremarkable.

**Differential diagnosis**

The differential diagnosis of CPVT will often include long-QT syndrome (LQTS), for example in children with syncope, ACA, or SCD during exercise, including swimming. If the resting ECG in non-diagnostic, exercise testing should be performed. The QTc-interval in the recovery phase of the exercise test may identify LQTS patients with a normal or borderline QTc-interval at rest. The presence of exercise-induced ventricular ecopythy beyond isolated VPBs favours a diagnosis of CPVT. Another important alternative diagnosis is Andersen-Tawil syndrome, which is caused by loss of function mutations in KCNJ2 in approximately 60% of cases. The classic phenotypic triad of this condition includes VA, periodic paralysis, and facial and limb dysmorphism, but these features are variably present. The most common cardiac manifestations are mild QTc prolongation, prominent U-waves, and VA, which may range from frequent VPBs to bidirectional or polymorphic VT. As such, KCNJ2 mutation-related polymorphic ventricular tachyarrhythmias, in the absence of other features of Andersen-Tawil syndrome, may very much mimic CPVT. However, distinction with other forms of CPVT is important, because patients with Andersen-Tawil syndrome show a much more benign course.

In patients with exercise-induced VAs, initially concealed structural heart disease, such as arrhythmogenic or hypertrophic cardiomyopathy, myocardial ischemia or mitral valve prolapse may be alternative diagnoses. Advanced cardiac imaging techniques and genetic testing may point towards a specific diagnosis. However, in some cases a particular diagnosis may reveal just after a particular period of close follow-up.

Apart from CPVT and Andersen-Tawil syndrome, bidirectional VT has also been reported in patients with digoxine intoxication, myocarditis, and myocardial infarction.

**Genetic diagnosis**

Genetic testing may be relevant to confirm the diagnosis in patients with a possible clinical diagnosis of CPVT, but is particularly important to identify asymptomatic relatives following identification of a CPVT-causative mutation in the index patient (Figure 3). In the recent Heart Rhythm Society/European Heart Rhythm Association consensus statement on genetic testing in inherited arrhythmia syndromes and cardiomyopathies, comprehensive CPVT genetic testing is recommended in index patients in whom “... a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient’s clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion”. In addition, it is stated that “RYR2 mutations may be regarded as a cause of adrenergically mediated idiopathic ventricular fibrillation, which may justify genetic testing in such instances”.

Hitherto over 130 unique, almost exclusively missense mutations in RYR2 have been reported. Mutations in RYR2 tend to affect three domains of the protein: the N-terminal
domain (codons 44-466; ~16% of mutations), the central domain (codons 2246-2534; ~20% of mutations) and the C-terminal channel-forming domain (codons 3778-4959; ~50% of mutations) (Figure 4). Hence, most laboratories apply a tiered targeting strategy for RYR2 mutational analyses, starting with the exons in which most have been identified. Mutations in RYR2 are identified in approximately 60% of patients with a definite clinical diagnosis of CPVT, 5 to 38% of patients with a possible clinical diagnosis of CPVT, 31% of patients with exertional syncope, and 15% of relatives of victims of adrenergic-mediated SCD or ACA with normal resting ECGs. Approximately 20% of RYR2 mutations are de novo.

Mutations in CASQ2 underlie a few percent of CPVT index cases. At present, 12 (putative) pathogenic mutations and three SNPs in CASQ2 have been identified. Although these mutations usually show an autosomal recessive inheritance pattern, thus predominantly causing CPVT in consanguineous families, it is unclear whether CASQ2 mutations, such as the R33X mutation, may also cause autosomal dominant transmission of the phenotype. In addition, compound heterozygous CASQ2 mutations in non-consanguineous families have been reported. Our center performs RYR2 mutational analyses in those exons in which mutations have been identified through a tiered strategy, and screens CASQ2 in consanguineous families. In negative cases from non-consanguineous families with a strong CPVT phenotype, the entire RYR2 gene and CASQ2 are screened. KCNJ2 is tested if there is an abundance of supraventricular- or ventricular ectopy present on Holter monitoring and/or a resting ECG that could correspond

Figure 3. RYR2 channel topology and localization of mutations and single nucleotide polymorphisms (based on Medeiros-Domingo et al.48). SNP indicates single nucleotide polymorphisms; SR, sarcoplasmic reticulum.
to the diagnosis of Andersen-Tawil syndrome, as recommended. TRDN will probably be added to arsenal of genetic testing in CPVT in the near future, in particular in consanguineous families. In relatives of mutation-positive index patients, predictive genetic testing of relatives with a 50% risk of carriership (cascade screening) is fairly straightforward. The only pitfall may be the presence of a pathogenic mutation in a mosaic form in the parents. This might result in a negative genetic result in the parents, whereupon the mutation in the index patient may be considered de novo and siblings (who have a 50% chance of being mutation-carrier) might not be tested. Genetic testing should be performed even in young children, possibly even at birth, because of the young age of manifestation of CPVT and its association with sudden infant death syndrome. Current knowledge suggests that it is safe to reassure and dismiss mutation-negative relatives from further cardiologic evaluation.
**PROGNOSIS AND TREATMENT**

**Risk stratification**

At present, risk stratification for the occurrence of arrhythmic events in CPVT patients is poorly defined. In contrast to other inherited arrhythmia syndromes such as LQTS and Brugada syndrome, we are currently unable to identify CPVT patients at low risk of arrhythmic events in whom treatment can be withheld. Thus, all clinically or genetically diagnosed CPVT patients should be actively treated.

In the largest patient series published, the risk of future arrhythmic events decreased with increasing age at diagnosis, while having experienced an ACA was associated with future fatal- or near-fatal events.\(^5^4\) CASQ2 mutation-carriers (N=7) were not at increased risk, but other reports suggest that these patients display a more complicated phenotype than RYR2 mutation-carriers or mutation-negative patients.\(^1^2, 3^3\)

New data suggest that among asymptomatic RYR2 or CASQ2 mutation-carrying relatives identified by cascade screening, those with a CPVT phenotype at the first exercise test have a higher risk of future cardiac events than those with no CPVT phenotype.\(^5^5\)

**Treatment**

**β-blocker therapy**

Ever since CPVT was first described, the strong relationship between VT to β-adrenergic activation and the efficacy of β-blocker therapy were recognized.\(^4, 5^6, 5^7\) As a consequence CPVT patients are advised to be cautious with practicing (competitive) sports, including swimming.\(^5^8\)

In the first comprehensive CPVT series published by Leenhardt et al. in 1995, it became apparent that β-blockers were the most effective drug therapy for reducing VAs during exercise testing or Holter monitoring and preventing arrhythmic events.\(^1\) In subsequently published series the range of arrhythmic events on β-blocker therapy has been variable.

Eleven studies describing a total of 403 CPVT patients were included in our systematic analysis on the overall efficacy of β-blocker therapy in CPVT (see Supplementary material and Table 1).\(^1, 6, 1^2, 3^2, 3^3, 3^5, 5^4, 5^9-6^2\)

As expected, mean age of patients in these studies was relatively young and no apparent gender predominance could be observed. Two-hundred sixty-seven patients (66%) were symptomatic when CPVT was diagnosed, and 255 patients (63% of total) harbored a RYR2 mutation, whereas 32 patients (8%) carried a CASQ2 mutation.

Out of the 403 patients, 354 (88%) had a β-blocker prescribed during follow-up and/or at time of an arrhythmic event (if any). Mean or median follow-up durations ranged from 20 months to eight years. Ten studies reported the proportion of CPVT patients experiencing an arrhythmic event, which ranged from 0 to 55% (Table 1).\(^1, 6, 1^2, 3^2, 3^3, 5^4, 5^9-6^2\)

The estimated overall 4- and 8-year arrhythmic event rates were 18.0% (95% CI, 7.7% to 28.9%) and 35.9% (95% CI, 15.3% to 56.5%), respectively (Figure 5 and Table 2).

Ten studies\(^1, 6, 1^2, 3^2, 3^3, 3^5, 5^4, 5^9-6^2\) reported the proportion of near-fatal and fatal arrhythmic events, ranging from 0 to 40% and 0 to 20%, respectively (Table 1). Estimated 4- and 8-year near-fatal arrhythmic event rates were 7.2% (95% CI, 3.1% to 11.3%) and 14.3% (95% CI, 6.1% to 22.5%), respectively (Figure 6 and Table 2). Fatal events occurred in 3.2% (95% CI, 1.6% to 4.8%) at 4-year and 6.4% (95% CI, 3.2% to 9.6%) at 8-year follow-up (Figure 7 and Table 2).
A few important factors may influence these results, so caution should be taken with interpretation. First, in one Japanese study daily β-blocker doses were significantly lower compared to the other studies that reported β-blocker doses, which might explain the high near-fatal and fatal event rates in that study. In addition, β-blocker doses were not reported in one study. Arrhythmic event rates excluding the Japanese study only and excluding both studies with low or unknown β-blocker doses are displayed in Table 2. No significant differences were observed.
Second, six studies described that at least one arrhythmic event could be attributed to poor drug compliance in general or at time of the arrhythmic event. Although drug compliance is one of the factors influencing drug efficacy, it could imply that VAs were actually well controlled in these patients when they did take their β-blocker.

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Lastly, in eight studies a minority of patients was treated with verapamil and/or flecainide, and/or underwent LCSD and/or ICD implantation in addition to β-blocker. Thus, the estimated event rates are not event rates on β-blocker exclusively, and the actual event rates on β-blockers only may be underestimated due to these additional treatment measures. Unfortunately it was not possible to study β-blocker efficacy in specific subgroups, such as age, gender, mutation status, and symptomatic versus asymptomatic patients, due to the low number of patients and lack of reported data.

<table>
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<th>Daily β-blocker dose</th>
<th>Therapy on top of β-blocker (number of patients)</th>
<th>Follow-up duration (years)*</th>
<th>Number of patients with arrhythmic events on β-blocker therapy</th>
<th>Number of patients with near-fatal arrhythmic events on β-blocker therapy</th>
<th>Minimal number of patients with arrhythmic events related to poor compliance</th>
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<td>Nadolol 40–80 mg</td>
<td>None</td>
<td>7 (2-16)†</td>
<td>3 (14%)</td>
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<td>Not reported</td>
<td>None</td>
<td>8 ± 6†</td>
<td>1 (7%)</td>
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<td>Mostly propranolol 4.8 mg/kg</td>
<td>ICD (6)</td>
<td>5.2 (5-11)†</td>
<td>8 (32%)</td>
<td>4 (16%)</td>
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<td>Acebutolol 200–400 mg, atenolol 100 mg</td>
<td>ICD (1)</td>
<td>6.5 (0.5-14)†</td>
<td>0</td>
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<td>Nadolol 1:2 mg/kg, metoprolol 1:3 mg/kg, propranolol 3:4 mg/kg</td>
<td>ICD (12)</td>
<td>3.3 ± 2.4 / 4.3 ± 2.5#</td>
<td>7 (37%) / 11 (55)#</td>
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<td>Propranolol 52±42, 64 ± 37, and 56 ± 24 mg††</td>
<td>Verapamil (3), mexiletine (2)</td>
<td>6.8 ± 4.9</td>
<td>Not reported**</td>
<td>9 (32%)</td>
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<td>ICD (2)</td>
<td>2 (2-37)</td>
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<td>Nadolol 1.6±0.9 mg/kg</td>
<td>Verapamil (6), ICD (16)</td>
<td>7.9 ± 4.9</td>
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<td>Propranolol 2:4 mg/kg</td>
<td>Verapamil (4), ICD (4)</td>
<td>2.5 ± 2.0</td>
<td>7 (47%)</td>
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<td>Metoprolol 125±50 mg, nadolol 77±34 mg</td>
<td>ICD (3)</td>
<td>1.8 (1:1-24)</td>
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<td>Atenolol 25–100 mg, nadolol 20–80 mg, bisoprolol 2.5–10 mg; mean equivalent bisoprolol dose = 8 mg</td>
<td>Verapamil (3), flecainide (5), LCSD (1), ICD (15)</td>
<td>6.2 ± 5.7</td>
<td>8 (32%)</td>
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<th>Study</th>
<th>Mean ± standard deviation or median (range), unless otherwise indicated;</th>
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*ICD indicates implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation.
Figure 5. Arrhythmic event curves. The solid line and its corresponding area indicate the proportion of patients with arrhythmic events and its corresponding 95% confidence interval based on a random-effects meta-analysis model. The data points represent the arrhythmic event rates of the individual studies (Table 1). The area of each data point is proportional to its number of patients and statistical weight. The two groups included in the study by Priori et al. (RYR2 mutation carriers and genotype-negative CPVT patients) are displayed separately, because data for the total study population are not provided.

Figure 6. Near-fatal arrhythmic event curves. The solid line and its corresponding area indicate the proportion of patients with near-fatal arrhythmic events and its corresponding 95% confidence interval based on a random-effects meta-analysis model. The data points represent the near-fatal arrhythmic event rates of the individual studies (Table 1). The area of each data point is proportional to its number of patients and statistical weight.

The study by Song et al., which included 10 non-genotyped CPVT patients in their single-center study on VT in children, was not included because the exact follow-up duration of this subgroup was not described. Although details on β-blocker therapy were not described either, their population seemed to remain symptomatic on β-blocker therapy. In addition to the four
children who suffered ACA (N=2) or SCD (N=2), some others were not well-controlled either, because three of them underwent LCSD, including one ICD patient who experienced electrical storm after panicking after an ICD shock. The appropriateness of the ICD shock is not described. Conversely, in the study by Allouis et al. all nine CPVT patients who received ß-blocker therapy were asymptomatic during an unknown follow-up duration.

Alternate chronic treatment options

**Calcium channel blockers**

Since calcium influx through the L-type calcium channels incites the so-called (increased) calcium-dependent calcium release through the defective or inappropriately regulated RYR2, the rationale for treating CPVT patients with the L-type calcium channel blocker verapamil

![Figure 7. Fatal arrhythmic event curves.](image)

The solid line and its corresponding area indicate the proportion of patients with fatal arrhythmic events and its corresponding 95% confidence interval based on a random-effects meta-analysis model. The data points represent the fatal arrhythmic event rates of the individual studies (Table 1). The area of each data point is proportional to its number of patients and statistical weight.

**Table 2. Event rates including all studies and excluding studies with low or unknown ß-blocker doses.**

<table>
<thead>
<tr>
<th>Studies included</th>
<th>4-year event rates</th>
<th>8-year event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arrhythmic</td>
<td>Near-fatal</td>
</tr>
<tr>
<td>All studies</td>
<td>18.0% (7.7-28.9)</td>
<td>7.2% (3.1-11.3)</td>
</tr>
<tr>
<td>Sumitomo et al&lt;sup&gt;10&lt;/sup&gt; (low</td>
<td>18.0% (7.7-28.3)</td>
<td>5.2% (2.0-8.5)</td>
</tr>
<tr>
<td>ß-blocker doses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumitomo et al&lt;sup&gt;10&lt;/sup&gt; and</td>
<td>19.8% (8.6-31.1)</td>
<td>5.9% (1.8-9.9)</td>
</tr>
<tr>
<td>Swan et al&lt;sup&gt;6&lt;/sup&gt; excluded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(low or unknown ß-blocker doses)</td>
<td></td>
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</tr>
</tbody>
</table>

Values are proportion (95% confidence interval).
is apparent. Moreover, the negative dromotrophic effect of verapamil could also positively contribute.

Swan et al. studied the efficacy of verapamil infusion (0.2 mg per kg of body weight) in addition to β-blocker therapy in reducing the VA burden during exercise testing in six CPVT patients carrying a RYR2 mutation. Verapamil significantly decreased the number of VPBs during the entire exercise test as well as the longest ventricular salvo, and increased the VA threshold rate as compared with the exercise tests before verapamil infusion and after a wash-out period. Rosso et al. treated six non-genotyped CPVT patients with exercise-induced ventricular ectopy despite maximally tolerated β-blocker doses with 240 mg verapamil daily (2 to 3 mg per kg body weight in children). After one to two weeks on combination therapy, exercise testing was repeated and a significant improvement in several VA parameters was observed. During short-term follow-up, two patients who had several episodes of syncope while on β-blocker therapy experienced one episode on combination therapy, whereas the other four patients (including one patient with multiple ICD shocks before verapamil was started) remained event-free. However, long-term verapamil did not prevent arrhythmic events in these patients. Three of these patients had clinically significant VAs during 37±6 months of follow-up.

Recently, Katz et al. studied the efficacy of several antiarrhythmic drugs in CASQ2 mutant mice and concluded that verapamil was most effective in reducing VAs induced by exercise and epinephrine infusion. Subsequently, 11 young CPVT patients homozygous for the CASQ2 mutation who remained symptomatic despite being treated with maximally tolerated doses of propranolol received the maximally tolerated dose of verapamil treatment. After one week, combination treatment resulted in a decrease in VA burden at exercise testing in five patients. Alcalai et al. also observed an important effect of verapamil in reducing VAs in their CASQ2 deficient mouse model.

In none of the three studies was a negative dromotrophic effect of verapamil observed, as the maximum heart rate was similar before and after verapamil in all studies.

Hayashi et al. reported four patients who remained event free during 1.6±0.6 years after verapamil was added to β-blocker therapy, but the indications for adding verapamil were not specified. Based on these data as well as our and others’ experiences, verapamil has not proven to be Columbus’ egg in CPVT patients with continuous VAs and/or symptoms on β-blocker therapy who require additional treatment. However, verapamil may be beneficial in some of these patients and/or in CPVT patients carrying a (specific) CASQ2 mutation.

**Flecainide**

An important new development in this field has been the discovery of the RYR2 blocking properties of the class 1c antiarrhythmic agent flecainide, which thereby can directly target the ‘molecular defect’ in CPVT. After promising results in in vitro and in vivo studies in (ventricular myocytes from) a CASQ2 knockout mouse model, flecainide was tested in two highly symptomatic CPVT patients (one RYR2 mutation and one CASQ2 mutation carrying patient). Flecainide dramatically reduced the VA burden during exercise testing in these patients. Next, the efficacy of flecainide was retrospectively evaluated in our relatively large multicenter study consisting of 33 mutation carrying CPVT patients. Flecainide had been started in these patients because of persistent physical or emotional stress-induced VAs and/or persistent
symptoms, while on β-blocker monotherapy or combined with calcium channel blockers. In 22 patients (76%) flecainide suppressed exercise-induced VAs either partially (N=8) or completely (N=14). Importantly, proarrhythmia as a result of flecainide was not observed. Median daily flecainide dose in patients in whom a decrease in VA burden was observed was 150 mg (2.3 mg per kg body weight; range, 100 to 300 mg [1.5 to 4.5 mg per kg body weight]). As a proportion of patients treated did not receive optimal β-blocker therapy (most often because of side-effects), a subgroup analysis was performed in patients who did receive optimal conventional therapy. Flecainide significantly improved the VA parameters in this subgroup to a similar extent as in the total study population, supporting the concept that flecainide’s point of action is independent from the degree of β-adrenergic receptor block.

During a median follow-up of 20 months (range, 12 to 40 months) no arrhythmic events occurred, except for one patient who experienced ICD shocks for polymorphic VAs, which was associated with very low flecainide levels. The study also included an RYR2 mutation carrier who presented with exercise-induced VT in 1981, and in whom flecainide has successfully suppressed exercise-induced VAs ever since.

Our findings were recently supported by a case of a female CPVT patient who did not tolerate β-blocker therapy and was successfully treated with flecainide,75 and a case of a severely symptomatic RYR2 mutation carrying 11-year-old boy.76 A concomitant advantage of treatment flecainide may be its efficacy in preventing supraventricular arrhythmias, which are associated with CPVT.1, 32, 33, 39, 62 Flecainide will probably play an important role in the treatment of CPVT patients. Yet, as previously commented,77 some issues are still unresolved, such as flecainide’s efficacy in preventing arrhythmic events long-term, its efficacy in genotype-negative CPVT patients, and whether flecainide could serve as first-line therapy (combined with β-blockers or even as monotherapy). Currently a randomized clinical trial comparing flecainide on top of β-blocker versus β-blocker monotherapy is ongoing to test the effect of flecainide prospectively (http://clinicaltrials.gov: NCT01117454).

Left cardiac sympathetic denervation

Decades before the efficacy of LCSD in CPVT patients was first reported,78 its beneficial results in patients with angina pectoris,79, 80 LQTS,81, 82 and post-myocardial infarction patients at high risk of SCD83 had been recognized. In this first publication on its efficacy in CPVT, the excellent follow-up results in three young CPVT patients in whom VAs could not be controlled by β-blocker therapy were reported, including two patients with a very long follow-up duration (20 and 10 years).78 This was followed by one case report84 and two case series,85, 86 all using video-assisted thoracoscopic LSCD. Atallah et al. described the results of LCSD in four CPVT patients who received recurrent ICD discharges for VT (N=3) or rapidly conducted supraventricular tachycardia (N=1) despite optimal drug therapy.85 One patient experienced one arrhythmic storm with recurrent ICD discharges in the first eight hours after the procedure, and remained event-free for the next two years. In the other three patients there were no VAs up to two months post-procedure. Collura et al. published the results of LCSD in two severely symptomatic CPVT patients.86 One patient experienced recurrent postoperative VAs leading to an extended hospital stay, but thereafter no other arrhythmic events occurred during 15 months of follow-up.
One case report suggested that the maximum benefit from LCSD may be several months instead of directly after the procedure, whereas another case showed that bilateral cardiac sympathetic denervation may (also) be effective. Pharmacologic sympathectomy using a high thoracic epidural catheter may be considered before performing LCSD to get information on its potential effectiveness.

In the 14 CPVT patients treated with LCSD that were collected by Odero et al., the result was favorable in 13 (93%). Although these initial results are encouraging, long-term follow-up has only been available in one more patient, who had a drastic decrease in appropriate ICD discharges during a 10-year follow-up. Hence, more data on the long-term efficacy of LCSD are required to determine its exact place in the therapeutic strategy in CPVT patients, including if the procedure's initial beneficial effects persist long term, and thus whether LCSD should be combined with drug therapy and/or ICD implantation.

The drawbacks of LCSD include potential complications, such as a transient or persistent Horner’s syndrome and pneumothorax, but the incidence of these complications is very low. Also, at the moment LCSD is not universally available, as an expert surgeon and dedicated instrumentation are required.

**Implantable cardioverter-defibrillators**

In the 2006 ACC/AHA/ESC Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention for Sudden Cardiac Death, a Class I recommendation was given for implantation of an ICD in addition to β-blocker therapy for CPVT patients who are survivors of ACA. A class IIa recommendation was given for ICD implantation in CPVT patients with syncope and/or documented sustained VT despite β-blocker therapy. More recently the Heart Rhythm UK Statement on Clinical Indications for ICDs in Adult Patients with Familial Sudden Cardiac Death Syndromes concurred with these recommendations, while adding LCSD as a therapeutic consideration before ICD implantation.

However, ICDs have been implanted much more liberal by the cardiological community before and after these guidelines were published. This was most probably caused by the high mortality rates in untreated CPVT patients and in CPVT patients with β-blocker therapy reported in the first case series, which gave CPVT a highly malignant reputation. Potentially this is a worrisome development, because ICDs may have harmful effect in CPVT patients. At least five cases have been described showing that both appropriate and inappropriate ICD shocks can trigger catecholamine release, subsequently resulting in multiple shocks, arrhythmic storm, and death, and as such ICD therapy does have a proarrhythmic potential. In a recent case report LCSD was performed simultaneously with ICD implantation to reduce the risk of such a fatal event.

In addition, many CPVT patients are young, in whom ICD implantation can lead to significant complications, and because of the increased prevalence of supraventricular arrhythmias, CPVT patients with an ICD are at increased risk of receiving inappropriate ICD shocks. In the series by Celiker et al. the number of patients (N=3) with appropriate ICD shocks was equal to the number of patients with inappropriate ICD shocks because of sensing errors (N=2), lead fracture (N=1, one of the patients with sensing errors), and lead migration. All four patients who received an ICD required psychological support because of signs of depression and anxiety. Inappropriate shocks can probably partly be prevented by careful ICD programming,
e.g. with one ventricular fibrillation zone with a detection interval of 240 beats per minute and (exceptionally) long detection intervals.

Given these serious drawbacks and the discovery of promising treatment alternatives on top of beta-blocker therapy, we propose a more conservative approach for ICD implantation in CPVT patients, probably even with regard to those who were diagnosed with CPVT after experiencing ACA (see Proposed treatment strategy).

Definition of failure of therapy
As ICD implantation is recommended in CPVT patients with syncope and/or documented sustained VT despite beta-blocker therapy, one may conclude that this imposes pharmacological failure. However, one study has had the statistical power to identify independent predictors for arrhythmic events in patients treated with beta-blockers. Predictors were treatment with beta-blockers other than nadolol (hazard ratio [HR], 3.12; 95% CI, 1.16 to 8.38; P=0.02), and a younger age at diagnosis (HR, 0.31 per decade; 95% CI, 0.14 to 0.69; P=0.004). In addition, the presence of couplets or more successive VPBs during exercise testing were significantly associated with future arrhythmic events (sensitivity, 0.62; specificity, 0.67). The association between provokable VT and risk of arrhythmic events was supported by the observations by Sy et al., who reported arrhythmic event rates of 36% in 22 CPVT patients with VT induced by exercise testing or epinephrine challenge and 0% in 5 patients without provokable VT. Yet, overall insufficient data are available to reliably identify high-risk patients. Indeed, persistent symptoms or VTs despite therapy should be considered a sign of treatment failure. Furthermore, albeit not perfectly predictive, it seems reasonable to intensify treatment with couplets or more successive VPBs during exercise testing, whereas solitary VPBs can probably be accepted.

Another important issue that may require a change in therapy of a CPVT patient is the presence of side-effects. In this relatively young patient population, fatigue and other side-effects due to beta-blockers may cause serious limitations in daily life and jeopardize therapeutic compliance.

Proposed treatment strategy
First, it is important to conclude that there is a lack of data to identify CPVT patients with such a low risk of arrhythmic events that would make treatment unnecessary. Thus, all phenotypically and/or genotypically diagnosed CPVT patients should receive appropriate therapy, although in clinical practice exceptions are (and probably can safely be) made in asymptomatic patients over approximately 60 years of age who are newly diagnosed by cascade screening.

Second, advising against participation in competitive sports and emphasizing the great importance of drug compliance are essential. In addition, CPVT patients should be informed that the use of sympathomimetic agents is contraindicated.

The first step in treating a CPVT patient should be a beta-blocker in the highest tolerable dose, preferably nadolol. Verapamil may be added to beta-blocker therapy, but addition of flecainide is preferred and more effective when beta-blocker therapy fails (step 2). In patients resistant to combination therapy with beta-blocker and flecainide, either LCSD should be performed or an ICD should be implanted (step 3). LCSD may be preferred when an expert surgeon is available to perform this procedure. To date it is unknown which pharmacologic regimen should be followed after a succesfull procedure, so it is recommended to continue beta-blocker therapy.
Every step and/or change in drug type or dose should probably be carefully monitored by exercise testing, and, if necessary and possible, Holter monitoring or ICD interrogation.

Future developments
Apart from the previously described developments that are being more widely introduced into patient care currently, some other treatment modalities may become available or may be introduced on a larger scale in CPVT patients in the near future. The class 1c antiarrhythmic agent propafenone may be another effective mechanism-based treatment option in difficult to treat CPVT patients. Propafenone successfully prevented further ICD shocks and exercise-induced CPVT in a patient from Turkey, who remained severely symptomatic after maximal drug therapy and LCSD. Because flecainide is not available in Turkey, propafenone was successfully attempted in this patient. Subsequent in vitro and in vivo studies showed that propafenone had similar RYR2 blocking properties to flecainide. As propafenone also contains β-receptor blocking properties, it may be an ideal drug in CPVT.

Dantrolene and the newly synthesized compounds S107 and K201 (JTV519) are also RYR2 channel inhibitors and prevented exercise- and epinephrine-induced VAs in CPVT mouse models. In addition, KN93, an inhibitor of calcium/calmodulin-dependent protein kinase II, was recently described as preventing VAs in a CPVT mouse model.

Another interesting observation is the CPVT patient in whom the selective serotonin reuptake inhibitor paroxetine combined with β-blocker therapy prevented ICD shocks during two years of follow-up, while this patient received two ICD shocks in the previous six months while treated with β-blocker only. However, the exact underlying mechanism of action remains to be clarified. Finally, pulmonary vein isolation (PVI) aimed to reduce supraventricular arrhythmias was successfully performed in a CPVT patient. This patient received inappropriate ICD shocks due to atrial fibrillation with a rapid ventricular response and therefore underwent PVI, which also decreased the number of VTs and PVCs on Holter registration. PVI may have decreased the sympathetic innervation, and may be an additional treatment option in patients resembling the case described.

Acute treatment
The most critical step in the acute management of sustained VT, VT storm or ventricular fibrillation in a CPVT patient (and in the absence of correctable inciting factors) may be to recognize that it concerns a CPVT patient, and the subsequent instruction to discontinue the standard epinephrine infusion in a resuscitation setting. Intravenous β-blocker therapy is considered first choice, analogous to VT storm of other etiology. General anesthesia is probably the last resort when β-blocker therapy is not effective. In one case report adenosine triphosphate and verapamil were effective in terminating epinephrine-induced VT during electrophysiological study.

CONCLUSIONS
Despite the advances that have been made in unravelling the genetic background, pathophysiology and clinical characteristics of CPVT, there is a need for additional research in
every aspect between bench and bedside. Important issues that need to be addressed include tools for risk stratification, in particular in asymptomatic CPVT associated mutation carriers, the role of genetic and environmental modifiers of the CPVT phenotype, and the genetic background of current genotype-negative cases.

ACKNOWLEDGEMENTS

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SUPPLEMENTARY MATERIAL

Literature search
We performed a literature search using the Medline and EMBASE databases from 1995 to February 18, 2011, including all studies that described the efficacy of ß-blocker therapy in CPVT patients. Search key words were: ‘Catecholaminergic polymorphic ventricular tachycardia’ and ‘CPVT’. The following inclusion criteria were used: published between 1995 and 2010, inclusion of ≥10 CPVT patients receiving ß-blocker therapy, and manuscript written in English. We did not consider abstracts presented at scientific meetings, since they are frequently not peer reviewed.

Meta-analysis
To provide an overall estimate of the efficacy of ß-blocker therapy in preventing arrhythmic events in CPVT patients, we performed a meta-analysis including the publications selected above. From each article we selected the following data: number of patients, number of probands and relatives, age at diagnosis, gender, number of symptomatic patients, genotypic status, number of patients treated with ß-blockers, follow-up duration, number of all arrhythmic, near-fatal arrhythmic, and fatal arrhythmic events, daily ß-blocker dose, number of patients receiving additional treatment, and number of arrhythmic events related to poor compliance.

Three outcomes were used to assess the efficacy of ß-blocker therapy: (1) all arrhythmic events, defined as physical or emotional stress-induced syncope, aborted cardiac arrest (ACA; including appropriate ICD discharge), and sudden cardiac death (SCD), (2) near-fatal arrhythmic events, defined as ACA and SCD, and (3) fatal arrhythmic events, defined as SCD.

Statistical analysis
The proportion of patients free of the outcome and the median or mean follow-up duration were used for meta-analytic calculations. Because of the large heterogeneity between the studies, a random-effects meta-analysis model was used. The pooled proportion of patients free of outcome as a function of time since diagnosis and 95% confidence intervals were estimated assuming a linear model. The analyses were performed using R (version 2.12.1, The R Foundation for Statistical Computing, Vienna, Austria).

Search results
After removing duplicates, a total of 401 articles were found. Further selection of relevant articles was done by reading the title and abstract. Ultimately 13 relevant studies were identified, of which two were excluded because follow-up duration was not described.63,64 Thus, 11 studies describing a total of 403 CPVT patients met our inclusion criteria (Table 1).1,6,12,32,33,35,54,59-62