An Actuarial Model of Arrhythmogenic Right Ventricular Cardiomyopathy and Life Insurance

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An actuarial model of arrhythmogenic right ventricular cardiomyopathy and life insurance

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ABSTRACT

Many countries ban insurers from using genetic test results in underwriting. One study [Howard, R. C. W. (2014). Report to CIA research committee: Genetic testing model: if the underwriters had no access to known results. Canadian Institute of Actuaries (CIA).] stated that such a ban in Canada would expose life insurers to adverse selection, causing premiums to increase by 12%. More than a quarter of this cost was attributable to a single disorder, Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). We model ARVC in a life insurance market, following the methodology of [Haçarız, O., Kleinow, T. & Macdonald, A. S. (2021). Genetics, insurance and hypertrophic cardiomyopathy. Scandinavian Actuarial Journal 2021, 54–81.], including ‘cascade’ genetic testing (CGT), so the rôle of family history in underwriting is modelled explicitly. We review (in the Appendix) the published epidemiology of ARVC, in particular the existence of an effective treatment, which we also include in our model. Our results are consistent with those of [Macdonald, A. S. & Yu, F. (2011). The impact of genetic information on the insurance industry: Conclusions from the ‘bottom-up’ modelling programme. Astin Bulletin 41(02), 343–376.] and [Haçarız, O., Kleinow, T. & Macdonald, A. S. (2021). Genetics, insurance and hypertrophic cardiomyopathy. Scandinavian Actuarial Journal 2021, 54–81.], namely, that in realistic scenarios premium increases would be negligible. We also consider the possibility of life settlement companies ‘gaming’ insurers by learning of adverse genetic test results, and conclude that to profit from purchasing policies from affected individuals, they would have to predict the future trajectory of the epidemiology of ARVC better than the epidemiologists themselves.

ARTICLE HISTORY

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KEYWORDS

Adverse selection; genetic epidemiology; cascade genetic testing; arrhythmogenic right ventricular cardiomyopathy; life insurance

1. Introduction

1.1. Life insurers and genetic test results

The use of genetic test results by life insurers has been controversial. Some argue that denying life insurers access to all available genetic information about policyholders leads potentially to increased costs due to adverse selection (Howard 2014). On the other hand, there are concerns that disclosure of genetic test results can lead to genetic discrimination, see Otlowski et al. (2012) or Tiller et al. (2017) for an Australian perspective.

In this study, we suppose that individuals who know about their own increased mortality risk might be more likely than usual to purchase life insurance cover. The higher risk is not priced for...
by the insurer, who is unaware of it, leading to losses. A measure of these losses is the proportional increase in premiums across the board that would be required to recoup the losses. In our view, this quantity is central to the discussion of the relevance of genetic testing to insurers.

We concentrate on a particular group of inherited cardiac diseases, called cardiomyopathies, and in particular on two that have been identified as highly significant contributors to adverse selection costs in a study by Howard (2014). In a previous paper, Haçarız et al. (2021), we modelled Hypertrophic Cardiomyopathy (HCM). In this paper, we apply the same ideas to model Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). The aetiology and epidemiology of ARVC are quite different from those of HCM, however, especially in one crucial respect; an effective treatment for ARVC is available, which must be included in the model.

For our quantitative analysis, we apply a stochastic model that allows us to model the joint life histories of members of a nuclear family, together with decisions they each make during their individual lifetimes. Our model takes into account modern genetic testing procedures called cascade genetic testing, and the choice of model parameters has been informed as much as possible by the epidemiology.

### 1.2. Cardiomyopathies, life insurance and adverse selection

Cardiomyopathies are inherited heart disorders, accounting for a significant proportion of cardiac disease and deaths at younger ages. They are caused by variants of any one of several individual genes and are mostly dominantly inherited.

In a Canadian study (Howard 2014), the two conditions mentioned above, HCM and ARVC, contributed the highest dollar losses arising from adverse selection, if life insurers were denied access to genetic test results. ARVC cost $111,141,682 and HCM cost $89,187,658, almost half of the total cost of $405,455,952 attributable to the thirteen disorders included in the study (see Section 4.2). For comparison, better-known single-gene disorders cost much less; Huntington disease $2,571,615 and inherited breast/ovarian cancer $5,363,834.

One reason for the high reported costs – overall about 12% of premium income – was an assumption that persons taking advantage of an adverse genetic test result would buy $1,000,000 of life cover, 10 times the normal amount. However, since this was the case for all 13 disorders, it cannot account for the large proportion of costs attributable to the cardiomyopathies.

Haçarız et al. (2021) introduced an actuarial model of HCM and genetic testing and found the cost of adverse selection to be generally much lower. Only by combining several extreme assumptions did the costs approach those in Howard (2014). The key to their approach was: (a) a detailed study of the epidemiology of HCM; and (b) an explicit dynamic model of genetic testing within families. In particular, they paid attention to the trajectory of the published genetic epidemiology, which tends to evolve from small studies of selected populations to larger studies of less selected populations, with important consequences for estimates of key parameters such as mortality hazards.

### 1.3. Plan of the paper

Since much of the genetical background not specific to HCM is in Haçarız et al. (2021), we refer the reader there. However, in Section 2 we present a short list of definitions essential to reading this paper. We then describe our model in Section 3. We assume that both insurers (in setting premiums) and family members (when purchasing life insurance) base their decisions on the information available to them. The cascade genetic testing model provides an explicit model of that information and in Sections 3.7 and 3.8, we describe how insurers and family members use it. Our results, showing costs under various adverse selection scenarios, are in Sections 4–7. In particular, Section 6 considers the effect of treatment by fitting an implantable cardioverter-defibrillator, which is a novel feature of this model. Our conclusions are in Section 8.
2. Genetic epidemiology: terminology

We define the following terms, which have these precise meanings throughout the paper.

(a) The ‘underlying condition’ is the physical change in the heart muscle or its regulatory system that defines the disorder. This may be present at birth or may develop later. It may be symptomatic or asymptomatic.

(b) ‘Onset’ marks the time at which the underlying condition is first present, at birth or later. A person is at risk of death due to the underlying condition only after onset.

(c) ‘Clinical diagnosis’ means the detection of the underlying condition. This may happen a long time after onset; that is, the disorder may be present but undetected, perhaps because there are no symptoms.

(d) ‘Genotype’ is the variant of a relevant gene present in an individual. Usually some rare variant is associated with the disorder and this is called a ‘deleterious variant’ (DV) (we understand that ‘mutation’ is falling out of use among geneticists).

(e) ‘Phenotype’ is the physical manifestation of the disorder. Here, we take it to be synonymous with the underlying condition. If the underlying condition is present, we say that the genotype has been expressed.

(f) ‘Penetrance’ is the proportion of carriers of a DV who have the underlying condition. It is usually less than 100%. If the underlying condition can develop after birth the penetrance is a function of age, which we denote by $F(x)$.

(g) ‘Proband’ is the first person in a family in whom the disorder is detected or a DV found by genetic testing. Either event reveals for the first time that a DV must ‘run in the family’.

We describe what we need of the epidemiology of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) in the Appendix. For quick reference, Table 1 lists where the main features can be found.

3. The model

3.1. A model of an individual’s life history

In Figure 1, we present our mathematical model of ARVC in a life insurance market, in which $i$ is a label representing a sub-population, related to genotype as described in Section 3.3. This uses the same framework as the HCM model in Haçariz et al. (2021), although their model was simpler in that onset and clinical diagnosis of the underlying condition were not represented as events, and there was no treatment. Appendix 1 of Haçariz et al. (2021) explained the general approach of using a multiple-state model to represent genetic variability, information and decision-making, and we refer the reader there.

The model represents events in a life history, as follows:

(a) At any time, buying life insurance.
(b) Onset of the underlying condition (ARVC).
(c) Clinical diagnosis after onset.

<table>
<thead>
<tr>
<th>Table 1. Main features of ARVC described in the Appendix.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature</td>
</tr>
<tr>
<td>Clinical features</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>Mode of inheritance</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>


Figure 1. A mathematical model of the life history of an individual, possibly at risk of ARVC, in a life insurance market. The label \( i \) \((= 0, 1, 2, 3, 4)\) indicates a sub-population defined by ARVC genotype, see Section 3.3. In \( \mu_i \) and \( \mu_{i} \), \( x \) refers to the duration in state \( i \) and state \( i4 \), respectively, since (if) a proband appeared in the family. ICD: Implantable cardioverter-defibrillator.

(d) Being fitted with an ICD after clinical diagnosis.
(e) Having a genetic test for an ARVC-related DV.
(f) Suffering a fatal ARVC-related event before or after an ICD implantation.
(g) Death from any other cause.

3.2. A model of a nuclear family’s life history

The key assumption is that the model in Figure 1 represents the life history of a single individual in a defined nuclear family, but we model the life histories of all the members of that nuclear family,
simultaneously in calendar time. Therefore some transition intensities can depend on what has happened to other family members. In this way, we model the effect of the information gained from knowing the family history. This information may be used: (a) by insurers, if allowed, in setting premium rates; and (b) by individuals, in deciding whether to take a genetic test, whether to buy life insurance, and if so the sum insured.

### 3.3. Sub-populations and family formation

Each individual is a member of one of five sub-populations, labelled \( i = 0, 1, 2, 3, 4 \). Sub-population 0 contains individuals who do not carry an ARVC-related DV. Sub-populations 2 and 4 contain individuals who carry known and unknown ARVC-related DVs, respectively. Sub-populations 1 and 3 are populated dynamically, as follows.

(a) We begin at calendar time 0, with a large number of individuals born in sub-populations 0, 2 and 4, in proportion to the population prevalences of ARVC genetic variants. Sub-populations 1 and 3 are empty.

(b) At calendar time 20, spouse-pairs form. Everyone still alive in sub-population 2 acquires a spouse of the opposite sex from sub-population 0, who is moved into sub-population 1. Likewise sub-population 3 is populated by the spouses of persons in sub-population 4.

(c) At calendar time 30, children are born to each surviving spouse-pair, the number being Poisson(\( \lambda \)) distributed (so possibly zero). Children are male with probability 1/2. Children with a parent who has an ARVC-related variant inherit it with probability 1/2, and are allocated to sub-population 1, 2, 3 or 4 accordingly. Our default assumption for mean family size is \( \lambda = 1.8 \), based on recent data for both the UK and USA, see Haçarız et al. (2021).

Individuals in sub-populations 0, 1 and 3 face identical biological risks, but both they and insurers may make different decisions depending on their family history.

### 3.4. Probands and family history

At calendar time 0, no-one in a family has clinical ARVC. A person may become a proband, by being the first family member to be clinically diagnosed with ARVC or to suffer a fatal ARVC event. The proband could be a parent or a child. As described in Section A.3, this event initiates CGT in the family, and it bestows a family history of ARVC upon every surviving family member.

### 3.5. The cascade genetic testing model

As soon as a proband appears, genetic testing becomes a possibility. First, the proband will be tested for known DVs. If one is identified, counselling and genetic testing will be offered to all the proband’s first-degree relatives. We use the same assumptions as Haçarız et al. (2021) for take-up rates of testing, that for one year after a proband has appeared, other family members have a constant intensity of \(- \log(1/2) = 0.6931472\) of transferring from an untreated to a tested state (so that each is tested with probability 1/2). We refer to Haçarız et al. (2021) and references therein for details.

In families in which an unknown DV is present, genetic testing is not possible, but family members will be recommended to undergo regular clinical screening.

CGT can ‘cascade’ beyond the nuclear family in which the proband appears. We do not model this directly, but Haçarız et al. (2021) noted that an effective proxy is to increase the value of \( \lambda \), since everyone offered testing under CGT carries the DV with probability 1/2.
3.6. An example

Here we give an example of a simulated family history in our population. We begin with a large number \( N \) of individuals age zero, with \( n_i \) in sub-population \( i \) (\( i = 0, 2, 4 \)) and none in sub-populations 1 and 3. Consider, say, a randomly chosen male in sub-population 2 who is still alive at age 20. He ‘marries’ a randomly chosen female from sub-population 0, who is immediately transferred to sub-population 1.

Now suppose both individuals are still alive at age 30, and they then have three children (a random draw from a Poisson distribution). The first is a boy who inherits the DV carried by the father. He is placed in sub-population 2. The second is a boy who does not inherit the DV. He is placed in sub-population 1. The third is a girl who also inherits the DV. She is placed in sub-population 2.

Suppose all five family members are alive at calendar time \( t = 50 \), when the parents are age 50 and the children are age 20. Suppose also that the father is then diagnosed with ARVC and the relevant DV is identified by a genetic test. The father is now a proband. CGT commences, and all three children are offered counselling and genetic testing. All three now have a family history of ARVC, whether they decide to be tested or not.

3.7. Information: premium rating

From an insurer’s point of view, there are two classes of family. Families in which no proband exists have no family history of ARVC; we call these underwriting class \( C^0 \) families. Families in which a proband exists (dead or alive) have a family history of ARVC; we call these underwriting class \( C^1 \) families. These are the two underwriting classes used for calculating premiums, if insurers are allowed to use family history.

We assume that insurers charge variable age-related premiums, payable continuously, rather than level premiums depending on age at entry. The premium is calculated as follows.

(a) The insurer calculates the occupancy probabilities in each model state at all future times, assuming there is no genetic testing and no adverse selection.
(b) The insurer allocates each ‘insured’ state to either class \( C^0 \) or class \( C^1 \).
(c) The premium rate per unit sum assured is the weighted average of all transition intensities from the ‘insured’ states in an underwriting class into ‘dead’ states, the weights being the occupancy probabilities from (a).

Our default assumption, when we bring genetic testing into the model, is slightly different from the above, reflecting practice in the UK. We include in underwriting class \( C^0 \) persons in sub-population 1 who have a family history of ARVC, but who have had a genetic test and therefore know they do not carry the DV. Also, an ‘untested’ non-carrier individual, whose carrier spouse becomes a proband, will be included in underwriting class \( C^0 \), ignoring the small possibility of both parents carrying an ARVC-related variant.

3.8. Information: insurance purchasing

At any time, each living uninsured individual, who is not themselves a proband, is in one of four information classes, which determine their insurance purchasing decisions.

(a) Class \( \zeta^n \): There is no proband and no family history.
(b) Class \( \zeta^{50} \): There is a proband but the individual has not had a genetic test.
(c) Class \( \zeta^0 \): The individual has had a genetic test which was negative.
(d) Class \( \zeta^{100} \): The individual has had a genetic test which was positive.
Intensities from ‘uninsured’ to ‘insured’ states, and possibly the sum insured, are defined to be functions of the information class, and thus reflect dynamically insurance-purchasing decisions, including adverse selection. Note that an ‘untested’ non-carrier individual, whose spouse becomes a proband, is assigned to class $\xi^n$.

### 3.9. A measure of adverse selection costs

We use the same measure of adverse selection costs as in Haçariz et al. (2021), namely, the expected present value (EPV) of the insurance loss under any adverse selection scenario, divided by the EPV of the premium income under the same scenario. We partition the population into $X$ and $Y$, where $X$ contains persons whose insurance purchases might change under adverse selection, and $Y$ contains everyone else. In the absence of adverse selection, the insurance losses and discounted premium income are $L_X$ and $P_X$ in population $X$, likewise $L_Y$ and $P_Y$ in population $Y$, and $E[L_X + L_Y] = 0$. Under adverse selection, the rates of premium per unit sum insured remain the same, but the loss and premium income in population $X$ change to $L_X^*$ and $P_X^*$, and our measure is then:

$$\frac{E[L_X^* + L_Y]}{E[P_X^* + P_Y]}.$$  

(1)

We compute $E[L_Y]$ and $E[P_Y]$ by solving the Kolmogorov forward equations and Thiele’s equations numerically. This is not possible for sub-populations 1 to 4, because some transition intensities depend dynamically on the family history, so we compute $E[L_X^*]$ and $E[P_X^*]$ by Monte-Carlo simulation. We refer to Haçariz et al. (2021) for details.

### 4. Results: adverse selection costs

#### 4.1. Baseline scenarios

##### 4.1.1. Prevalences of genetic variants

Based on Section A.4, we assume the prevalence of DVs to be 1/1000. Although this in fact is based on the prevalence of clinical ARVC, doing so is conservative for our purposes. However, there is some disagreement about this in the literature and we will test alternatives in Section 7.1. Based on Section A.2, we also assume 70% of DVs to be ‘known’ and 30% ‘unknown’.

##### 4.1.2. Penetrance of DVs

We conservatively estimate the penetrance of clinical ARVC at age $x$ ($10 < x \leq 60$) to be $F(x) = 0.01x$, relying on the reported data in Quarta et al. (2011), see Section A.5. The associated annual hazard rate of onset at age $x$ is then $F'(x)(1 - F(x))^{-1}$.

##### 4.1.3. ARVC-related mortality

Howard (2014) (who used a discrete-time model) assumed annual mortality ($q_x$) of 2.3% per year. Our model is in continuous time, and all rates or hazards mentioned from now on are transition intensities. In view of the discussion in Section A.6, a mortality hazard of 2.3% per year seems excessive, and possibly based on outdated epidemiology. The comment by Corrado et al. (2017b), quoted in Section A.6.1, suggests that an annual hazard of less than 1% would be appropriate, and comparison of Tables A1 and A3 suggests that allowance should be made for implanting an ICD. Table A2 also suggests that mortality in relatives of the proband is lower, possibly because of early treatment. It seems reasonable to either: (a) allow explicitly for ICD implantation; or (b) assume lower mortality
in relatives of the proband; but not both at the same time. Our (conservative) baseline assumption is an annual ARVC hazard of 1%, with initially no allowance for ICD treatment.

4.1.4. Population mortality
The population mortality rates (not related to ARVC) are assumed to be those of the Life Tables, United States (US), 2013 (Arias et al. 2017), males and females.

4.1.5. Clinical diagnosis
We have no empirical data on clinical diagnosis. This is particularly important in sub-populations 3 and 4 with unknown ARVC variants, because clinical screening will be recommended in place of genetic testing. We assume an annual hazard rate of clinical diagnosis of 0.20, which is conservative for our purposes, see Section 5.6 for details. For simplicity, this intensity is assumed to be the same before and after a proband exists in a family.

4.1.6. Insurance purchasing
Following Haçarız et al. (2021), and earlier authors, such as Macdonald & Yu (2011), we assume a ‘normal’ annual rate of insurance purchase of 0.05. Later we will use a rate of 0.01 to represent a smaller life insurance market (Section 5.2) or as a proxy for a larger market in which lapse is significant. We then superimpose higher annual purchase rates of 0.10 or 0.25, depending dynamically on the information class (Section 3.8) to represent mild or severe adverse selection, respectively. Specifically, persons in information classes $\xi^{50}$ and $\xi^{100}$ purchase at the higher rate. In the baseline all sums insured are £1. However, we will consider the impact of higher sums insured in those information classes in Section 5.3. If insurers may use family history, they may charge the premium rate for underwriting class $C_1$. If insurers may not use family history, there is only one underwriting class, $C_0$.

The force of interest is assumed to be 5% per annum.

4.2. Comparison with Howard (2014)
Based on the dollar costs attributed to ARVC in Howard (2014) (see Section 1.2), namely, $111,141,682 out of a total adverse selection cost of $405,455,952, added to estimated premium income of $3.5 billion (in 2012, in Canada), premium increases of about 3% in our model would be comparable to the costs in Howard (2014). In that study, ARVC and HCM were the two most costly disorders, contributing almost half of the total cost.

4.3. Baseline adverse selection costs
We summarise the baseline assumptions in Table 2 and present the premium increases under the baseline adverse selection scenarios in Table 3. The necessary premium increases to redeem the baseline adverse selection costs are very small, all below 0.02%. Allowing insurers to use family history reduces the premium increases by a factor of about 3 and 2.5 under mild and severe adverse selection, respectively.

In the remainder of the paper, we explore the sensitivity of adverse selection costs to the key parameters in Table 2. In particular we ask: under what conditions might adverse selection costs be material?

Note that the percentage premium increases under no adverse selection are zero to four decimal points even though we estimate some of the insurance losses (Equation (1)) by Monte-Carlo simulation. This is because we have to make a small adjustment to the premium rates to allow for the higher mortality of DV carriers before the assumed reproductive age of 30.
Table 2. Baseline assumptions for the model parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of non-ARVC variants in the general population at age 20</td>
<td>0.999</td>
<td>4.1.1</td>
</tr>
<tr>
<td>Prevalence of ARVC variants in the general population at age 20</td>
<td>0.001</td>
<td>4.1.1</td>
</tr>
<tr>
<td>Prevalence of known DVs in the ARVC population at birth</td>
<td>70%</td>
<td>4.1.1</td>
</tr>
<tr>
<td>Prevalence of unknown DVs in the ARVC population at birth</td>
<td>30%</td>
<td>4.1.1</td>
</tr>
<tr>
<td>Hazard rate of penetrance of ARVC per annum at ages 10–60</td>
<td>( \mu_0 )</td>
<td>4.1.2</td>
</tr>
<tr>
<td>Hazard rate of clinical diagnosis before a proband exists per annum for all ages</td>
<td>0.20^b</td>
<td>4.1.5</td>
</tr>
<tr>
<td>Hazard rate of clinical diagnosis after a proband exists per annum for all ages</td>
<td>0.20^b</td>
<td>4.1.5</td>
</tr>
<tr>
<td>Proportion of individuals having an ICD treatment at all ages</td>
<td>0%^c</td>
<td>6.1</td>
</tr>
<tr>
<td>Hazard rate of fatal ARVC before an ICD treatment per annum for all ages</td>
<td>1%</td>
<td>4.1.3</td>
</tr>
<tr>
<td>Hazard rate of fatal ARVC after an ICD treatment per annum for all ages</td>
<td>0.28%</td>
<td>4.1.3</td>
</tr>
<tr>
<td>Hazard rate of all other death per annum for all ages</td>
<td>( \mu_A )</td>
<td>4.1.4</td>
</tr>
<tr>
<td>Hazard rate of testing in one year at ages 0–70 since (if) a proband exists</td>
<td>( \mu_T )</td>
<td>3.5</td>
</tr>
<tr>
<td>Hazard rate of normal insurance purchase per annum at ages 20–60</td>
<td>5%</td>
<td>4.1.6</td>
</tr>
<tr>
<td>Normal sum assured</td>
<td>51</td>
<td>4.1.6</td>
</tr>
<tr>
<td>Force of interest per annum</td>
<td>5%</td>
<td>4.1.6</td>
</tr>
</tbody>
</table>

^a \( \mu_0^D = F'(x)(1 - F(x))^{-1} \) where \( F(x) = 0.01x \), estimated penetrance of clinical ARVC at age \( x \).

^b This is a conservative assumption for our purposes, please see the details in Section 4.1.5.

^c This represents a proportion of annual rate of clinically diagnosed individuals.

^d \( \mu_A \) is estimated from the reported mortality rates in Life Tables, United States, 2013 (Arias et al. 2017).

^e \( \mu_T \) = 0.6931472, which represents 50% of untested individuals taking up genetic testing in one year.

Table 3. Percentage increases in premiums due to baseline adverse selection scenarios (Section 4.3 and Table 2).

<table>
<thead>
<tr>
<th>Selection</th>
<th>Mean premium increase and 95% QI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Family history disallowed</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>0.0000</td>
</tr>
<tr>
<td>Mild</td>
<td>0.0076</td>
</tr>
<tr>
<td>Severe</td>
<td>0.0164</td>
</tr>
</tbody>
</table>

Note: The 95% quantile intervals (QI) are in respect of the Monte-Carlo estimation of mean EPVs of cashflows in the ARVC families (see Section 3.9).

5. Factors amplifying adverse selection costs

5.1. Family history disallowed in underwriting

We noted, in Section 4.3, that when insurers are not allowed to use family history, the baseline adverse selection costs increased by a factor of between about 2.5 and 3 (for HCM the factor was about 2.7, see Haçariz et al. (2021)).

5.2. A smaller life insurance market

We assume (as a baseline) a ‘normal’ insurance purchase rate of 0.05 per annum, representing a large life insurance market. To represent a small market we use an annual purchase rate of 0.01. The purchase rate for individuals in information classes \( \xi^{50} \) and \( \xi^{100} \) under ‘mild’ and ‘severe’ adverse selection is twice (0.02) and 25 times (0.25) the normal purchase rate, respectively. We present the results in Table 4, ‘Purchase Intensity’. The main result is that severe adverse selection results in percentage premium increases about five or six times greater than in the larger market. However, they are still fractions of one percent.

5.3. Higher sums insured under adverse selection

We so far assumed that, under adverse selection, individuals in information classes \( \xi^{50} \) and \( \xi^{100} \) increase their purchases of insurance, but they still choose the ‘normal’ sum insured. We consider here
### Table 4. Mean percentage increases in premiums (95% QIs omitted) due to changing parameters (resulting in amplification of adverse selection costs) in baseline adverse selection scenarios (Section 5).

<table>
<thead>
<tr>
<th>Section</th>
<th>Varied parameter</th>
<th>Family history disallowed</th>
<th>Family history allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adverse selection</td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>5.2</td>
<td>Purchase Intensity(^a)</td>
<td>0.05</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01</td>
<td>0.0000</td>
</tr>
<tr>
<td>5.3</td>
<td>Sum Insured(^b)</td>
<td>1 ×</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 ×</td>
<td>0.0160</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 ×</td>
<td>0.0480</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 ×</td>
<td>0.1438</td>
</tr>
<tr>
<td>5.4</td>
<td>Proportion Tested(^c)</td>
<td>50%</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99%</td>
<td>0.0000</td>
</tr>
<tr>
<td>5.4</td>
<td>CGT Extension(^d)</td>
<td>(\lambda = 1.8)</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\lambda = 3.0)</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\lambda = 5.0)</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\lambda = 7.0)</td>
<td>0.0000</td>
</tr>
<tr>
<td>5.5</td>
<td>ARVC Mortality(^e)</td>
<td>1%</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3%</td>
<td>0.0000</td>
</tr>
<tr>
<td>5.6</td>
<td>Clinical Diagnosis(^f)</td>
<td>0.02</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.05</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.10</td>
<td>0.0000</td>
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<tr>
<td></td>
<td></td>
<td>0.20</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.30</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.75</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.00</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.50</td>
<td>0.0000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.00</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Note: 'None' refers to the 'normal' purchase intensity. \(^a\)Annual purchase intensities in a large and smaller life insurance markets, respectively.

\(^b\)Increased sums insured taken out by adverse selectors.

\(^c\)A higher rate of uptake of genetic testing, with approximately 99% acceptance instead of 50%.

\(^d\)Extending cascade genetic testing (CGT) as a proxy beyond the first generation by increased values of \(\lambda\), the mean number of children.

\(^e\)ARVC-related annual mortality hazard rates.

\(^f\)Annual hazard rate of clinical diagnosis of those who have suffered onset of ARVC.

Higher sums insured for these classes. Following the notation in Section 3.9 and Haçarız et al. (2021), \(L_X^{*}\) is decomposed into two parts:

\[(a) \quad L_X^{*(1)}, \text{ representing those in population } X \text{ who purchase higher sums insured}; \text{ and } \]
\[(b) \quad L_X^{*(2)}, \text{ representing those in population } X \text{ who purchase the normal sum insured}. \]

Therefore, our measure in Equation (1) can be modified, where the individuals contributing to \(L_X^{*(1)}\) purchase \(n\) times the normal (unit) sum insured, as follows:

\[
\frac{E[nL_X^{*(1)} + L_X^{*(2)} + L_Y]}{E[nP_X^{*(1)} + P_X^{*(2)} + P_Y]},
\]
Table 4, ‘Sum Insured’, presents the premium increases where individuals in information classes $\zeta^{50}$ and $\zeta^{100}$ purchase sums insured of 2, 4, and 10 times normal, in a large life insurance market. Premium increases are still small, but the magnitude of them is much higher than that of in the other parameters in this table.

### 5.4. *More cascade genetic testing*

In our model, more genetic testing can happen in two ways.

(a) *A higher rate of uptake of testing.* Table 4, ‘Proportion Tested’, presents the premium increases if 99% of ‘untested’ individuals (instead of 50%, see Section 3.5) accept testing within a year of a proband appearing in the family. This corresponds to a testing hazard rate of 4.60517.

(a) (1) When family history is disallowed, the premium increases are almost identical because we assume that persons in information classes $\zeta^{50}$ and $\zeta^{100}$ behave in the same way under adverse selection.

(b) (2) When family history is allowed, the premium increases are slightly higher because we allow ‘negatively’ tested individuals to disclose their test results and pay the premium rates of underwriting class $C^0$ (see Section 3.7).

(b) *CGT extends beyond the nuclear family.* If we increase $\lambda$, this approximates CGT extending beyond the nuclear family, since anyone offered a test under CGT is known to be a DV carrier with probability 1/2. We present the results in Table 4, ‘CGT Extension’, for $\lambda = 1.8; 3.0; 5.0; \text{and } 7.0$. The last of these represents CGT spreading through about three other related nuclear families, and the premium increases are about twice those with $\lambda = 1.8$.

### 5.5. *Higher ARVC-related mortality*

Based on Section 4.1.3, we calculate premium increases with an ARVC-related annual mortality hazard rate of 2.3% before ICD treatment (instead of 1%). We present the results in Table 4, ‘ARVC Mortality’. The premium increases are about twice those with the mortality hazard rate of 1%.

### 5.6. *Rate of clinical diagnosis*

Haçarız et al. (2021) assumed that clinical diagnosis of HCM followed the occurrence of an HCM-related event. This was conservative, as it reduced the number of individuals with a pre-existing condition. There were also no clearly defined treatments for HCM that could be included in the model.

In the case of ARVC, there is an effective treatment – ICD implantation – and sufficient epidemiology to estimate the reduction in mortality. To include treatment in the model, we have to include clinical diagnosis also. Unfortunately, there are no empirical data on clinical diagnosis, and even if there were, it is a factor that is likely to vary from place to place and from time to time.

Instead we investigate a wide range of intensities of clinical onset. Table 4, ‘Clinical Diagnosis’, presents the premium increases under the baseline scenario of adverse selection (see Section 4.3), with annual intensities of clinical diagnosis ranging from the very low (0.02) to the very high (2.00).

(a) A higher rate of clinical diagnosis has two effects, acting in opposite directions. First, it creates probands in a larger number of families. When family history is allowed in underwriting, this increases the number of individuals offered the underwriting class $C^1$ premium rates. Second, it creates a larger number of uninsured individuals with a pre-existing condition.

(b) Table 4, ‘Clinical Diagnosis’, shows that premium increases rise quite quickly until the annual intensity of clinical onset is about 0.20, and thereafter do not change very much. This is
intuitively reasonable, because an annual intensity of 0.20 is very high, and a large proportion of ‘susceptible’ individuals (those who have suffered onset of ARVC) will be clinically diagnosed within a few years.

(c) We repeated this exercise in other scenarios, including the smaller market and higher sums insured taken out by adverse selectors, with similar results. We omit these to save space.

As a result, we adopt an annual intensity of clinical diagnosis of 0.20 in all our scenarios.

5.7. Worst cases

With the help of the results so far, we explore the worst case scenarios in our model. Table 5 presents the premium increases under ‘severe’ adverse selection in the smaller market, where cascade genetic testing is firstly extended through the first generation ($\lambda = 1.8$) then later through more generations ($\lambda = 7.0$) and individuals in information classes $\xi^{50}$ and $\xi^{100}$ purchase ten times the normal sum insured. With an ARVC-related annual mortality hazard rate of 1%, and family history allowed, the premium increases are still below 1%. But, the premium increases are above 1% in other cases, reaching about 4%, with an ARVC-related annual mortality hazard rate of 2.3%, $\lambda = 7.0$, and family history disallowed. We present these figures merely to test the utmost limits of our model; we do not suggest they are realistic.

6. Treatment by ICD implantation

6.1. ICD implantation reduces mortality

A noteworthy distinction between this study and Haçariz et al. (2021) is that an effective treatment for ARVC is available, namely the implantation of an ICD. The large reductions in mortality were summarised in the studies shown in Table A3.

We estimate ARVC-related mortality after ICD treatment by aggregating the deaths and exposures of all the studies listed in Table A3, resulting in an annual hazard rate of 0.28%.

6.2. Rates of ICD implantation

Calkins et al. (2017) presents three risk categories (high, intermediate, and low), based on symptoms of ARVC, to determine the urgency of ICD implantation. This might be justified by the recent studies estimating the time between clinical diagnosis of ARVC and any ICD implantation.

(a) In Schuler et al. (2012) and Kimura et al. (2016), the median time from clinical diagnosis to ICD implantation was 1.5 and 2.4 months, respectively. In the former, all patients were

<table>
<thead>
<tr>
<th>ARVC Mortality</th>
<th>$\lambda$</th>
<th>Mean Premium Increase and 95% QI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Family history disallowed</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>1.0</td>
<td>1.8</td>
<td>1.0327 (0.7814, 1.3209)</td>
</tr>
<tr>
<td>1.0</td>
<td>7.0</td>
<td>2.1256 (1.8774, 2.3757)</td>
</tr>
<tr>
<td>2.3</td>
<td>7.0</td>
<td>4.1815 (3.8720, 4.4976)</td>
</tr>
</tbody>
</table>

*ARVC-related annual mortality hazard rates.
*The mean number of children in which $\lambda = 7.0$ represents extensive cascade genetic testing.
severely symptomatic. In the latter, the authors suspected the presence of referral bias in their sample.

(b) Otherwise, in Maupain et al. (2018), the median time was 2 years, and in Mazzanti et al. (2016), an ICD was implanted in 81 ARVC patients over a total follow-up of 1432 person-years. Possibly, these study populations were more heterogeneous than those in (a).

In Figure 1, ICD treatment is represented as a transition between states. This is helpful chiefly because it fixes the logical order of events, but we have no means of estimating the transition intensity. However, it is reasonable to assume that treatment, if recommended, will be carried out as soon as possible after clinical diagnosis. We therefore assume that a fixed proportion of individuals are fitted with an ICD immediately on clinical diagnosis. The proportions we assume are 0% (the baseline), 25%, 50%, 75% and 100%. We present the results in Table 6, ‘ICD Treatment’. The adverse selection costs are steadily reduced with increasing use of ICD treatment. With 100% treated, premium increases are reduced by a factor of about two compared to no ICD treatment at all.

Table 6. Mean percentage increases in premiums (note that 95% QIs are omitted) varying parameters resulting in diminished adverse selection costs in baseline adverse selection scenarios (Sections 6 and 7).

<table>
<thead>
<tr>
<th>Varied Parameter</th>
<th>Family history disallowed</th>
<th>Family history allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section</td>
<td>Biological/ Behavioural</td>
<td>Purchase Intensity Insured</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.2 ICD Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p_{ICD} = 0%$</td>
<td>0.05</td>
<td>1 x</td>
</tr>
<tr>
<td>$p_{ICD} = 25%$</td>
<td>0.05</td>
<td>1 x</td>
</tr>
<tr>
<td>$p_{ICD} = 50%$</td>
<td>0.05</td>
<td>1 x</td>
</tr>
<tr>
<td>$p_{ICD} = 75%$</td>
<td>0.05</td>
<td>1 x</td>
</tr>
<tr>
<td>$p_{ICD} = 100%$</td>
<td>0.05</td>
<td>1 x</td>
</tr>
</tbody>
</table>

7.1 Prevalence

| Prevalence | 0.1% | 0.05 | 1 x | 0.0000 | 0.0076 | 0.0164   | 0.0000 | 0.0025 | 0.0066   |
| 0.02%      | 0.05 | 1 x |    | 0.0000 | 0.0015 | 0.0032   | 0.0000 | 0.0005 | 0.0012   |
| 0.7%       | 0.05 | 1 x |    | 0.0000 | 0.0010 | 0.0021   | 0.0000 | 0.0003 | 0.0008   |

7.2 Selection Bias

| Selection Bias | $p_{ICD} = 0\%$ | 0.05 | 1 x | $-0.0697$ | $-0.0620$ | $-0.0533$ | $-0.0710$ | $-0.0739$ | $-0.0750$ |
|               | $p_{ICD} = 50\%$ | 0.05 | 1 x | $-0.0855$ | $-0.0797$ | $-0.0731$ | $-0.0871$ | $-0.0920$ | $-0.0953$ |
|               | $p_{ICD} = 100\%$| 0.05 | 1 x | $-0.0919$ | $-0.0982$ | $-0.0937$ | $-0.1038$ | $-0.1109$ | $-0.1165$ |
|               | 0.01 | 1 x |    | $-0.0595$ | $-0.0475$ | $-0.0327$ | $-0.0607$ | $-0.0686$ | $-0.0950$ |
|               | 0.01 | 10 x|    | $0.0688$ | $0.1880$ | $0.9724$  | $-0.1535$ | $-0.2310$ | $-0.4836$ |
|               | 0.01 | 10 x|    | $0.0249$ | $0.1192$ | $0.7162$  | $-0.1996$ | $-0.3035$ | $-0.7523$ |
|               | 0.01 | 10 x|    | $0.0190$ | $0.0456$ | $0.4454$  | $-0.2463$ | $-0.3820$ | $-1.0349$ |

7.3 Information Class

| Information Class | $\zeta_{50,\zeta_{100}}$ | 0.05 | 1 x | 0.0000 | 0.0076 | 0.0164 | 0.0000 | 0.0025 | 0.0066 |
|                  | $\zeta_{100}$         | 0.05 | 1 x | 0.0000 | 0.0027 | 0.0056 | 0.0000 | 0.0017 | 0.0037 |
|                  | $\zeta_{50,\zeta_{100}}$| 0.01 | 1 x | 0.0000 | 0.0120 | 0.0923 | 0.0000 | 0.0023 | 0.0312 |
|                  | $\zeta_{100}$         | 0.01 | 1 x | 0.0000 | 0.0043 | 0.0328 | 0.0000 | 0.0024 | 0.0206 |
|                  | $\zeta_{50,\zeta_{100}}$| 0.01 | 10 x| 0.1284 | 0.2477 | 1.0327 | 0.0202 | 0.0432 | 0.3240 |
|                  | $\zeta_{100}$         | 0.01 | 10 x| 0.0460 | 0.0891 | 0.3724 | 0.0255 | 0.0499 | 0.2306 |

Note: ‘None’ refers to the ‘normal’ purchase intensity. $p_{ICD}$ represents a constant proportion of clinically diagnosed individuals immediately having an ICD implantation.

* Different prevalences of ARVC-related DVs. The last case (0.7%), penetrance is adjusted to maintain the clinical incidence of ARVC.

It assumes that the insurer calculates premiums in the $C_1$ underwriting class assuming an ARVC-related mortality hazard rate of 2.3%, without ICD treatment at all, when then actual mortality hazard rate is 1%, with/without ICD treatment.

Inquires premium increases where individuals in information class $\zeta_{50}$ purchase insurance at ‘normal’ rate and sum insured under adverse selection.
7. Other factors diminishing adverse selection costs

7.1. Different DV prevalences

Based on the opinion of Corrado et al. (2017a) (see Section A.4), we will assume a lower DV prevalence of 1/5000. Alternatively, based on the results of Lahtinen et al. (2011) (see Section A.4), we will assume a higher prevalence of known DVs of 1/200, which would increase to at least 1/140 \( \approx 0.7\% \) when non-desmosomal and unknown DV carriers (Section 4.1.1) were included.

The higher prevalence of 0.7\% models ‘silent’ ARVC DVs with the same observed clinical outcomes as with the baseline prevalence of 0.1\%. To achieve this, approximately, we multiply the penetrance \( F(x) \) by a factor 0.1/0.7 \( \approx 0.14 \). Then, if the incentive to purchase insurance is shaped by genetic test results, adverse selection costs should diminish.

We present the results in Table 6, ‘Prevalence’. With prevalence 0.02\% the premium increases are diminished by a factor of about five. With prevalence 0.7\% (and adjusted penetrance) they are diminished by a factor of about eight.

7.2. The effect of selection and ascertainment bias

The epidemiological literature for genetic disorders is subject to selection and ascertainment biases, meaning that epidemiologists can study only that population which comes to their attention. (See Hodge (2002) and the references therein for the large literature on this subject.) Risks of onset and death for these disorders might be different (probably lower) if a representative sample of the whole population could be studied. Doing so would be very expensive, because of the rarity of these disorders, but as the epidemiology evolves over time, these biases might diminish. Always our past risk estimates turn out to be high.

Remarkably, if insurers calculate premiums relying on outdated epidemiology, they might even profit from adverse selection. For instance, suppose the insurer based premiums on an ARVC-related annual mortality hazard of 2.3\% with no ICD treatment (relying on Howard (2014)) but in reality the mortality hazard rate is 1\%, possibly with ICD treatment. We present the results in Table 6, ‘Selection Bias’. The adverse selection costs are reversed. Specifically when family history is allowed, insurers make a profit in each scenario, the more so as adverse selection becomes more extreme.

7.3. The purchasing behaviour of information class \( \zeta^{50} \)

Assuming the persons in information class \( \zeta^{50} \) behave in the same way as persons in information class \( \zeta^{100} \) is conservative for our purposes. In reality, would they really purchase insurance beyond meeting their needs (especially extremely high sums insured) since they know only that they are a DV carrier with probability 1/2? Here we consider the possibility that individuals in information class \( \zeta^{50} \) purchase less insurance than those in information class \( \zeta^{100} \). Table 6, ‘Information Class’, presents the premium increases when individuals in information class \( \zeta^{50} \) behave ‘normally’ while those in information class \( \zeta^{100} \) purchase insurance at a higher rate and with higher sums insured. When family history is disallowed, the adverse selection costs are reduced by a factor of about three, and when family history is allowed, by a factor of about between 1.4 and 1.8.

8. Conclusions

We modelled premium increases arising from adverse selection caused by life insurers being barred from access to adverse genetic test results for ARVC-related DVs. Our conclusions are as follows.

(a) Premium increases are very small, less than 0.1\%, in most scenarios, certainly in those we would regard as realistic. This is consistent with the results of Macdonald & Yu (2011) and Haçariz et al. (2021).
(b) Premium increases seem to be smaller than those found for HCM in comparable scenarios (Haçarız et al. 2021). Howard (2014) found the opposite.

(c) The largest premium increase was about 4.2%, broadly comparable with Howard (2014). However, in addition to assuming that ‘adverse selectors’ took out ten times the normal sum insured, we also had to make the following extreme assumptions: a small insurance market; an ARVC-related mortality hazard of 2.3%; no ICD treatment; and extensive CGT ($\lambda = 7.0$). Simply assuming that insurers could use family history reduced the premium increases to about 1.2%. A key factor relied on by Howard (2014) was the assumption of widespread purchasing of extremely high sums insured under adverse selection. Lombardo (2018), modelling the adverse selection cost in the US life insurance market using the same epidemiological assumptions as Howard (2014), also said: ‘The U.S. Model results produced and presented in this report are very sensitive to the testing rate and face amount assumptions. They are highly subjective and move the U.S. Model results proportionately. Although it is reasonable to assume genetic testing rates in the U.S. will increase over time, and that some individuals with particular genetic characteristics will seek out higher-than-average insurance amounts, it is at present difficult to validate these two assumptions.’

(d) If insurers calculate premiums based on an ‘outdated’ epidemiology, subject to significant selection bias, when in fact the risks of onset and death are lower, they may be substantially protected against the worst of adverse selection. In particular, this would destroy the business model of any life settlement companies that attempted to originate new insurance policies based on genetic test results.

Disclosure statement

No potential conflict of interest was reported by the authors.

References


Howard R. C. W. (2014). Report to CIA research committee: Genetic testing model: If the underwriters had no access to known results. Canadian Institute of Actuaries (CIA).


Appendix. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

A.1 Clinical features

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited heart muscle disorder. See Basso et al. (2009), Calkins et al. (2017) and references therein for what follows. It substantially causes ventricular arrhythmias, which might lead to various symptoms, such as palpitations, syncope (fainting), and, not so commonly, fatal sudden cardiac arrest (SCA). It might also cause heart failure, whose progressive forms might require heart transplant or lead to death. In general, clinical onset does not arise before ages 10–12 or after age 60. However, it is a major cause of fatal SCA in young people and athletes, who are otherwise healthy.

A.1.1 Terminology

Several names have been used for the same disorder. Basso et al. (2009), Corrado et al. (2017b), and Corrado et al. (2017a) are good references for the evolving terminology. The first extensive clinical description of ARVC was given by Marcus et al. (1982). At that time, it was called ‘arrhythmogenic right ventricular dysplasia’ because it was thought to be congenital. The later discovery of the genetic substrate of ARVC led to the term ‘cardiomyopathy’ (inherited heart muscle disorder) being used. It was also discovered that left ventricular involvement is common, so the broader term ‘arrhythmogenic cardiomyopathy’ has also been used. As a result, the names ARVD/C, ARVC/D, and AC are found in the literature.

The literature uses the term sudden cardiac death (SCD) rather than fatal SCA. We prefer to use the latter because, in many studies of HCM, endpoints included non-fatal events (see Haçarız et al. 2021). This issue does not arise in studies of ARVC (Section A.6.1), but we retain the term SCA for consistency with the earlier actuarial study.

A.1.2 Diagnosis

Clinical practitioners have mainly used 1994 and recently 2010 Task Force Criteria (TFC), for the diagnosis of clinical ARVC (see McKenna et al. 1994 and Marcus et al. 2010, respectively). Diagnosis is made by means of electrocardiogram (ECG), imaging machines (for example, echocardiogram and magnetic resonance imaging (MRI)), biopsy findings, family history, and positive genetic test results. However, no ‘gold standard’ has been established yet. For example, Gandjbakhch et al. (2018) said:

The diagnosis of ARVC/D is probably the most challenging in the field of inherited cardiomyopathies because of the absence of specific unique diagnostic criteria, its variable expressivity, and its incomplete penetrance in relatives. The main problem is that a definitive pathological diagnosis is only given by a seldom available historical study obtained by biopsy, surgery, or necropsy. Indirect evidence can be obtained by multimodal cardiac imaging studies. ECG data show RV disease, but other RV cardiomyopathies may alter it in a similar way, such as myocarditis, which interacts with ARVC/D, sarcoidosis, or the rare Uhl’s disease.

This has an impact on estimating prevalence, penetrance, and mortality associated with clinical ARVC (Section A.4(b)).

A.2 Genetics

ARVC largely follows autosomal dominant inheritance, meaning that one affected parent passes the DV to any child with 50% probability. Its genetic substrate is commonly explained by variations in desmosomal genes, which encode proteins involved in the attachment of heart muscle cells (myocytes). We follow two studies reporting DV frequencies in ARVC patients:

(a) Gandjbakhch et al. (2018) stated that up to about 60% of ARVC patients carry known DVs, the majority in the desmosomal genes PKP2 (20–45%), DSG2 (4–15%), DSP (1–13%), DSC2 (1–7%) and JUP (0–1%), and a minority in non-desmosomal genes related to clinical ARVC. The genetic substrate of the remaining 40% or so of patients is unknown.


(b) Corrado et al. (2019) stated that 40–50% of ARVC patients carry DVs in desmosomal genes, ordered in decreasing frequency as follows: PKP2, DSP, DSC2, DSG2, JUP. Another 20–30% had DVs in non-desmosomal genes, and other genetic and non-genetic disorders mimicking clinical ARVC. Another 10–20% had causes unknown (not clearly indicated, but presumably unknown gene DVs).

A.3 Cascade genetic testing (CGT)

To the best of our knowledge, Haçarız et al. (2021) is the only paper which models cascade genetic testing (CGT) with an application to life insurance. We refer there for more details. The general CGT procedure can be described as follows.

(a) A person is diagnosed with ARVC in a family in which its presence is previously unknown. This person is called the 'proband' or 'index patient'.
(b) The proband is genetically tested for the presence of known DVs associated with ARVC.
(c) If the proband carries a known DV, all first-degree relatives are offered genetic testing to identify if they carry the same DV. Those who test negative are presumed not to be at risk. Those who test positive are recommended to undergo clinical screening at intervals, and if necessary are treated.
(d) If the proband does not carry a known DV, all first-degree relatives are recommended to undergo clinical screening at intervals, and if necessary are treated.
(e) The process above can be extended to other first-degree relatives of those first-degree relatives of the proband who test positive for a known DV, and thus can spread through an extended family in a 'cascade' fashion.
(f) Note that nobody offered genetic testing is obliged to agree to take it up.

A.4 Prevalence

ARVC is a rare disorder with a clinical prevalence estimated to be between 1/5000 and 1/1000 in the general population (Peters et al. 2004, Basso et al. 2009, Andreasen et al. 2013). The first of these studies reported 80 clinically affected persons ages 22–91 (mean age 45.6) in a hospital in Quedlinburg serving a population of 80,000, hence a population prevalence of 1/1000. This has been discussed in the literature.

(a) Sen-Chowdhry et al. (2010) underlines that 1/1000 might be an underestimate, saying ‘… milder cases frequently go unrecognised and nonclassic subtypes were not incorporated and biventricular arrhythmogenic cardiomyopathy are commonly misattributed to dilated cardiomyopathy.’
(b) Corrado et al. (2017a) said ‘Because the initial manifestation may be sudden cardiac death (SCD), undiagnosed patients probably make up an additional 30% in most populations. Yet, the prevailing opinion by most specialists in this area is that the prevalence is closer to 1:5000. The discordance may be related to frequent misdiagnoses. One report on the rate of misdiagnosis for AC identified that only 24 of 89 (27%) people referred to a tertiary center met the diagnostic criteria established at the time.’

On the other hand, prevalence of ARVC-related DV carriers might be higher than prevalence of clinically affected ARVC patients, as was the case with HCM. Hall et al. (2018) estimated the population prevalence of ARVC-related DV carriers to be between 1/257 and 1/845 based on the analysis of 138,632 unrelated individuals. In a Finnish study, 29 out of 6,334 unselected individuals carried desmosomal gene variants associated with ARVC, a prevalence of 1/200 (Lahtinen et al. 2011). In Section 7.1, we see how this might significantly reduce adverse selection costs.

A.5 Penetrance

Quarta et al. (2011) estimate the penetrance \( F(x) \) (see Section 2) to be about 0% at age 10; 10% at age 20; 20% at age 30; 35% at age 40; 50% at age 50; 55% at age 60; and 60% afterwards, meaning that the penetrance is incomplete (less than 100%). Although clinical studies of ARVC predominantly include men (Section A.6), this study did not distinguish gender.

A.6 Mortality

We present estimates of the annual hazard rate of ARVC-related mortality in Tables A1, A2, and A3, based on many studies published between 1987 and 2017, see Basso et al. (2012) and Calkins et al. (2017) for these studies. The important distinction is whether or not an implantable cardioverter-defibrillator (ICD) has been fitted, as this has a dramatic effect on mortality. We estimate an ARVC-related annual mortality hazard rate \( \mu_x \) at age \( x \) by the number of recorded deaths \( d_x \) divided by the total person-years exposed to risk \( E_x \) among a group of \( n_x \) observed individuals labelled with the age \( x \). The age label \( x \) refers to a range of ages within which the assumed hazard rate is assumed to be constant.
The average age at entry into the studies in Tables A1, A2, and A3 was between the third and fourth decades of life. The studies predominantly included men.

A.6.1 Evolution of the estimated mortality hazard

The annual ARVC-related mortality hazard ranged from zero to 4.56% (although the highest annual hazard, see Table A3, results from a study reporting a single death). Corrado et al. (2017b) noted that:

The estimated overall mortality varies among studies, ranging from 0.08 to 3.6% per year. The mortality was initially overestimated because it was based on studies at tertiary referral centres, which predominantly included high-risk patients. Recent studies of community-based patient cohorts have shown that the long-term outcome for treated index patients and family members is favourable (annual mortality, < 1%).

A.6.2 Relatives of probands

There is some evidence that at-risk relatives of probands (those who carry an identified DV) might have lower ARVC-related mortality, which might be explained by them receiving early clinical care. See Nava et al. (2000) in Table A1 and Groeneweg et al. (2015) in Table A2. The latter is a large study following up 1,001 individuals (439 probands, 5% of whom were asymptomatic, and 562 of their relatives, 82% of whom were asymptomatic). Table A2 shows that the annual mortality hazard of ARVC in probands might be about twice that of their relatives.

Table A1. Annual hazard rate of ARVC-related mortality ($\mu_x$) based on the clinical cohorts who had (or not) an ICD treatment during a follow-up period.

<table>
<thead>
<tr>
<th>$\bar{x} \pm s_x$</th>
<th>$n_x$</th>
<th>Men %</th>
<th>ICD %</th>
<th>$d_x$</th>
<th>$E^*_x$</th>
<th>$\mu_x$ %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>15</td>
<td>67</td>
<td>n/a</td>
<td>3</td>
<td>132.00</td>
<td>2.27</td>
<td>Blomström-Lundqvist et al. (1987)</td>
</tr>
<tr>
<td>33 ± 13.5</td>
<td>58</td>
<td>83</td>
<td>n/a</td>
<td>4</td>
<td>510.40</td>
<td>0.78</td>
<td>Leclercq &amp; Coumel (1989)</td>
</tr>
<tr>
<td>36</td>
<td>22</td>
<td>86</td>
<td>n/a</td>
<td>3</td>
<td>235.40</td>
<td>1.27</td>
<td>Canu et al. (1993)</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
<td>27</td>
<td>15</td>
<td>3</td>
<td>140.00</td>
<td>2.14</td>
<td>Kullo et al. (1995)</td>
</tr>
<tr>
<td>40 ± 13</td>
<td>72</td>
<td>68</td>
<td>n/a</td>
<td>3</td>
<td>324.00</td>
<td>0.93</td>
<td>Berder et al. (1995)</td>
</tr>
<tr>
<td>31 ± 13</td>
<td>132</td>
<td>n/a</td>
<td>n/a</td>
<td>1</td>
<td>1122.00</td>
<td>0.08</td>
<td>Nava et al. (2000)a</td>
</tr>
<tr>
<td>31.8 ± 14.4</td>
<td>130</td>
<td>77</td>
<td>n/a</td>
<td>21</td>
<td>1053.00</td>
<td>2.00</td>
<td>Hulot et al. (2004)b</td>
</tr>
<tr>
<td>30 ± 12</td>
<td>69</td>
<td>52</td>
<td>68</td>
<td>3</td>
<td>414.00</td>
<td>0.72</td>
<td>Dalal et al. (2005)c</td>
</tr>
<tr>
<td>44 ± 14</td>
<td>61</td>
<td>72</td>
<td>39</td>
<td>10</td>
<td>279.38</td>
<td>3.58</td>
<td>Lemola et al. (2005)d</td>
</tr>
<tr>
<td>44.8 ± 16.5</td>
<td>313</td>
<td>63</td>
<td>11</td>
<td>9</td>
<td>2660.50</td>
<td>0.34</td>
<td>Peters (2007)</td>
</tr>
<tr>
<td>32.6 ± 14.1</td>
<td>50</td>
<td>66</td>
<td>40</td>
<td>9</td>
<td>n/a</td>
<td>2.82</td>
<td>Watkins et al. (2009)</td>
</tr>
<tr>
<td>35 ± 15</td>
<td>96</td>
<td>68</td>
<td>13</td>
<td>12</td>
<td>1024.32</td>
<td>1.17</td>
<td>Pinamonti et al. (2011)e</td>
</tr>
<tr>
<td>48 ± 15</td>
<td>30</td>
<td>63</td>
<td>43</td>
<td>1</td>
<td>170.10</td>
<td>0.59</td>
<td>Li et al. (2012)</td>
</tr>
<tr>
<td>38</td>
<td>88</td>
<td>68</td>
<td>0</td>
<td>12</td>
<td>800.80</td>
<td>1.50</td>
<td>Brun et al. (2016)f</td>
</tr>
<tr>
<td>46 ± 15</td>
<td>110</td>
<td>75</td>
<td>35</td>
<td>18</td>
<td>1254.00</td>
<td>1.44</td>
<td>Kimura et al. (2016)g</td>
</tr>
<tr>
<td>38 ± 18</td>
<td>301</td>
<td>58</td>
<td>27</td>
<td>31</td>
<td>1789.00</td>
<td>1.73</td>
<td>Mazzanti et al. (2016)h</td>
</tr>
</tbody>
</table>

Notes: ICD: Implantable cardioverter-defibrillator. $x$: Age (years). $\bar{x}$: Average age at entry. $s_x$: Standard deviation. $n_x$: Total number of individuals in a clinical cohort at entry. $d_x$: Total number of ARVC-related deaths during a follow-up period. $E^*_x$: Central exposure to risk. 'Men' and 'ICD' percentages were rounded to integer values. This table is based on Basso et al. (2012), Table 2 and Calkins et al. (2017), Table 1. $n_x = 132$ were clinically affected family members obtained from 37 probands (19 diagnosed at autopsy).

The authors noted that this study might likely have included high-risk ARVC patients. The 1/3 and 2/3 of ARVC-related deaths was caused by fatal SCA and heart failure, respectively.

Heart transplantation (HT) was evaluated as an endpoint. The authors noted that this study might likely have had a ‘selection bias’ based on their clinical cohort consisted of ‘highly selected’ ARVC patients.

Heart transplantation (HT) was evaluated as an endpoint.

$\bar{x} \pm s_x$ was 38.4±15.9; 35.9±14.8; 47.5±12.2 for $n_x = 88$ (22; 54; 12, respectively).

Heart transplantation (HT) was included into the cause of ARVC-related death. Males were found to expose higher risk of ventricular arrhythmias than women.

Endpoints were ‘a first life-threatening arrhythmic event’ (fatal SCA, resuscitated SCA, syncopal ventricular tachycardia or electrical storm), or ‘cardiovascular mortality’. Of $n_x = 301$, 23 (15 initially observed fatal SCA and 8 lost to follow up) were not followed-up. If this is taken into account; then we obtain $\mu_x = 0.89\%$, which was reported to be 0.8% in the study.
Table A2. Annual hazard rate of ARVC-related mortality ($\mu_x$) between probands and their relatives, who had (or not) an ICD treatment during a follow-up period, from Groeneweget al. (2015).

<table>
<thead>
<tr>
<th>Family Member</th>
<th>DV Carrier</th>
<th>Entry</th>
<th>$\bar{x} \pm s_x$</th>
<th>$n_x$</th>
<th>Men %</th>
<th>ICD %</th>
<th>$d_x$</th>
<th>$E^c_x$</th>
<th>$\mu_x$ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband</td>
<td>Yes</td>
<td>Alive</td>
<td>n/a</td>
<td>416</td>
<td>n/a</td>
<td>84</td>
<td>22</td>
<td>3512</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dead</td>
<td>n/a</td>
<td>23</td>
<td>n/a</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 ± 14</td>
<td>439</td>
<td>64</td>
<td>84</td>
<td>45</td>
<td>3512</td>
<td>1.28</td>
</tr>
<tr>
<td>Relative</td>
<td>Yes</td>
<td>Alive</td>
<td>n/a</td>
<td>385</td>
<td>n/a</td>
<td>23</td>
<td>6</td>
<td>1636</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dead</td>
<td>n/a</td>
<td>24</td>
<td>n/a</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 ± 19</td>
<td>409</td>
<td>45</td>
<td>23</td>
<td>30</td>
<td>1636</td>
<td>1.83</td>
</tr>
<tr>
<td>Probable</td>
<td>Alive</td>
<td>n/a</td>
<td>152</td>
<td>n/a</td>
<td>23</td>
<td>30</td>
<td>0</td>
<td>459</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td>n/a</td>
<td>1</td>
<td>n/a</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>n/a</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Notes: Probable DV carriers represent first degree-relatives of probands with unknown DV(s). Please see the headings in Table A1.

\[ ^a \text{For } n_x = 439, 409, 153, \text{ the respective mean follow-up times (unreported) are assumed to be 8, 4, 3 years from the reported mean ages at initial and last follow-up, leading to } E^c_x = 3512, 1636, 459, \text{ in each group that also assumed to be same for the } n_x = 416, 385, 152 \text{ alive individuals at entry in these groups.} \]

Table A3. Annual hazard rate of ARVC-related mortality ($\mu_x$) based on the clinical cohorts who had an ICD treatment were followed-up.

<table>
<thead>
<tr>
<th>$\bar{x} \pm s_x$</th>
<th>$n_x$</th>
<th>Men %</th>
<th>$d_x$</th>
<th>$E^c_x$</th>
<th>$\mu_x$ %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 ± 19</td>
<td>12</td>
<td>58</td>
<td>1</td>
<td>21.96</td>
<td>4.56</td>
<td>Link et al. (1997)</td>
</tr>
<tr>
<td>36 ± 18</td>
<td>9</td>
<td>89</td>
<td>0</td>
<td>24.03</td>
<td>0.00</td>
<td>Tavernier et al. (2001)</td>
</tr>
<tr>
<td>40 ± 15</td>
<td>132</td>
<td>70</td>
<td>3</td>
<td>435.60</td>
<td>0.69</td>
<td>Corrado et al. (2003) (^a)</td>
</tr>
<tr>
<td>43 ± 16</td>
<td>60</td>
<td>82</td>
<td>4</td>
<td>396.00</td>
<td>1.01</td>
<td>Wichter et al. (2004)</td>
</tr>
<tr>
<td>36 ± 13</td>
<td>42</td>
<td>52</td>
<td>0</td>
<td>147.00</td>
<td>0.00</td>
<td>Roguin et al. (2004)</td>
</tr>
<tr>
<td>35.9</td>
<td>48</td>
<td>63</td>
<td>0</td>
<td>124.80</td>
<td>0.00</td>
<td>Hodgkinson et al. (2005) (^b)</td>
</tr>
<tr>
<td>36 ± 14</td>
<td>67</td>
<td>52</td>
<td>2</td>
<td>294.80</td>
<td>0.68</td>
<td>Piccini et al. (2005) (^c)</td>
</tr>
<tr>
<td>35.6 ± 18</td>
<td>106</td>
<td>67</td>
<td>0</td>
<td>511.98</td>
<td>0.00</td>
<td>Corrado et al. (2010)</td>
</tr>
<tr>
<td>31.9 ± 11.9</td>
<td>84</td>
<td>46</td>
<td>1</td>
<td>397.32</td>
<td>0.25</td>
<td>Bhonsale et al. (2011) (^d)</td>
</tr>
<tr>
<td>n/a</td>
<td>26</td>
<td>81</td>
<td>2</td>
<td>278.20</td>
<td>0.72</td>
<td>Schuler et al. (2012) (^b)</td>
</tr>
<tr>
<td>40 ± 14</td>
<td>108</td>
<td>60</td>
<td>0</td>
<td>356.40</td>
<td>0.00</td>
<td>Link et al. (2014)</td>
</tr>
<tr>
<td>33.6 ± 13.9</td>
<td>312</td>
<td>52</td>
<td>3</td>
<td>2745.60</td>
<td>0.11</td>
<td>Orgeron et al. (2017) (^d)</td>
</tr>
</tbody>
</table>

Note: Please see the headings in Table A1. This table is based on Basso et al. (2012), Table 4 and Calkins et al. (2017), Table 2. \(^a\) Heart transplantation (HT) was evaluated as an endpoint.

\(^b\) Mean follow-up time (unreported) was assumed to be as same as median follow-up time.

\(^c\) Of $n_x = 67$, 12 were noted to be with ‘probable ARVC’.

\(^d\) An ICD intervention and heart transplant were evaluated as endpoints.

### A.6.3 ICD treatment

Tables A1 and A2 state the proportion of subjects who had ICD treatment, when known. Table A3 is based on studies in which all subjects had ICD treatment. It shows that ICD treatment is effective in reducing ARVC-related mortality, although many of the studies are small.