GENETICS, INSURANCE AND ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

By Oytun Haçarız†, Torsten Kleinow† and Angus S. Macdonald†

ABSTRACT

Many countries ban insurers from using genetic test results in underwriting. One study, (Howard 2014) 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 (2020) and Haçarız et al. (2020), including ‘cascade’ genetic testing (CGT), so the rôle of family history in underwriting is modelled explicitly. We review 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 & Yu (2011), Haçarız (2020) and Haçarız et al. (2020), 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.

KEYWORDS

Adverse Selection, Genetic Epidemiology, Cascade Genetic Testing, Arrhythmogenic Right Ventricular Cardiomyopathy, Life Insurance

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1. Introduction

1.1 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 mutations in any one of several individual genes and are dominantly inherited.

In a Canadian study (Howard 2014) two of these conditions, namely Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) and Hypertrophic Cardiomyopathy (HCM), 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 4.3). 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 reported relatively high 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, ten times the normal amount. However, since
this was the case for all thirteen disorders, it cannot account for the large proportion
of costs attributable to the cardiomyopathies. To explore that, we must turn to the
epidemiology.

1.2 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. In our model, a person is at risk of death due to ARVC after onset but not
before.

(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 mutation’
(DM).

(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 DM 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 $F(x)$.

For example, in HCM the underlying condition is left-ventricular wall thickness of
13 to 15 mm or more. Reaching this threshold defines onset, and the expression of
the genotype as the phenotype. This can be detected by an echocardiogram, but unless there
is a reason to investigate (symptoms develop, there is an incidental finding, or a close
relative is diagnosed with HCM) no clinical diagnosis will be made. (See Haçarız et al.
(2020).)

1.3 Genetic Epidemiology: Before Genetic Testing

Haçarız (2020) reviewed the epidemiological literature on HCM and found the follow-
ing broad features, which apply also to other cardiomyopathies.

(a) Genetic disorders are often first identified, then studied, in small populations at
severely elevated risk, such as patients at an advanced stage of treatment. Estimates
of mortality rates can be extremely high.

(b) Over time, larger populations are studied, though this usually means tens or hun-
dreds rather than thousands. The individuals studied are still selected, but less so;
perhaps healthy persons shown by clinical screening to have the underlying condition.
Estimated mortality rates fall significantly.

(c) The prevalence of the disorder is estimated by clinical screening of an unselected
population for presence of the underlying disorder. For a rare disorder the outcome
may be a handful of cases among several thousand individuals.

(d) The penetrance $F(x)$ is often hard to estimate because data are usually left-truncated.

Epidemiologists are well aware of biases associated with this process. Selection bias arises because study populations are selected only if the disorder is present (except, above, in estimating prevalence). Also ascertainment bias may arise (see Hodge (2002) and references therein) because of the manner in which affected families come to the attention of researchers.

1.4 Genetic Epidemiology: After Genetic Testing
DNA-based genetic testing has opened up some new avenues.

(a) Genes associated with a disorder may be identified, and then specific mutations in a gene. It is common that mutations in different genes may cause the same disorder, likewise different mutations within the same gene. Sometimes different mutations have different effects, such as early onset or late onset (that is, different penetrances).

(b) The prevalences of mutations may be estimated, usually with much uncertainty.

(c) A significant proportion of mutations may remain unidentified. Genetic testing is not possible in families carrying unknown mutations.

(d) Identifying a relevant mutation may be important clinically, especially if the underlying disorder is difficult to diagnose. For example, it is much harder to make a definite diagnosis of ARVC (see Section 2.1.2) than HCM.

1.5 Genetic Epidemiology: Disease Prevalence versus Mutation Prevalence
The prevalence of mutations can be estimated based on unselected populations. The results can be a surprise. For example, the prevalence of HCM has been estimated to be about 0.2% (Maron et al. 1995) based on screening for the underlying condition. However, the prevalence of HCM-related mutations has been estimated to be about 0.6% (Bick et al. 2012). Since this study could find only known mutations, thought to account for about 2/3 to 3/4 of the total, the true prevalence of HCM-causing mutations could be close to 1%. As we shall see, something similar seems to be true of ARVC (see Section 2.4).

1.6 Family History, Genetic Testing and Treatment
Population-based genetic testing for a rare disorder is costly, so the form of genetic testing in use for cardiomyopathies is cascade genetic testing (CGT, described in Section 2.3). In CGT, predictive testing is offered only to blood relatives of someone who has been tested and shown to carry a known DM. So the condition for testing to be offered is very similar to the underwriting definition of the presence of a family history.

The primary purpose of CGT is to detect DMs in blood relatives who may be asymptomatic and either:

(a) have not developed the underlying condition but can be clinically screened at intervals in future, or;

(b) have developed the underlying condition and can be offered treatment.

If effective treatment is available, mortality may be greatly reduced, see Sections 2.6.2 and 2.6.3.
1.7 Consequences for Actuarial Models

Actuaries have shown interest in genetic testing primarily because of fears of adverse selection, should insurers be denied access to genetic test results. Quantitative models depend almost entirely on the published epidemiological literature. It is therefore important to understand:
(a) the trajectory of that literature, as described in Section 1.3;
(b) what stage in that trajectory might have been reached in any study on which the actuary relies;
(c) what the true position might be if selection and ascertainment biases were absent; and
(d) what mortality rates apply before and after any treatment.

Most important are the facts that: (a) penetrance and mortality may both be overstated in the presence of selection and ascertainment biases; and (b) that mortality in the presence of a DM may be much lower than mortality in the presence of the underlying condition. Failure to allow for these may lead to adverse selection costs being overstated. Moreover, if a life insurer based premium rates on overstated penetrance and mortality rates, there would be two consequences.
(a) Losses from adverse selection would be reduced, or even reversed, becoming a source of profit for insurers.
(b) Any third party, such as a life settlement company, attempting to ‘game’ the life insurance industry by financing adverse selection, might suffer losses.

In short, anyone hoping to make money out of adverse selection ought to be sure that they understand the epidemiology better than the epidemiologists themselves.

1.8 Plan of the Paper

Hacaricz (2020) studied the epidemiology of HCM, and developed a model of CGT for HCM. Our purpose is to study ARVC similarly. Its aetiology (Section 2) differs markedly from that of HCM, and we develop a different model (Section 3). In particular, an effective treatment exists. We describe the model of CGT in Section 3.4. 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 CGT model provides an explicit model of that information and in Sections 3.5 and 3.6 we describe how insurers and family members use it. Our results, showing costs under various adverse selection scenarios, are in Sections 4, 5, and 6, and our conclusions are in Section 7.

2. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

2.1 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.

2.1.1 Terminology

Several names have been used for the same disorder. Basso et al. (2009), Corrado et al. (2017), 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 Haçarz et al. (2020)). This issue does not arise in studies of ARVC (Section 2.6.1), but we retain the term SCA for consistency with the earlier actuarial study.

2.1.2 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 histological 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 2.4(b)).

2.2 Genetics

ARVC largely follows autosomal dominant inheritance, meaning that one affected parent passes the DM to any child with 50% probability. Its genetic substrate is commonly explained by mutations in desmosomal genes, which encode proteins involved in the attachment of heart muscle cells (myocytes). We follow two studies reporting mutation frequencies in ARVC patients:
(a) Gandjbakhch et al. (2018) stated that up to about 60% of ARVC patients carry known mutations, 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 mutations in desmosomal genes, ordered in decreasing frequency as follows: PKP2, DSP, DSC2, DSG2, JUP. Another 20–30% had mutations 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 mutations).

2.3 Cascade Genetic Testing (CGT)

To the best of our knowledge, Haçarız (2020) and Haçarız et al. (2020) are the only studies which model cascade genetic testing (CGT) with an application to life insurance. We will refer to these studies 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 mutations associated with ARVC.
(c) If the proband carries a known mutation, all first-degree relatives are offered genetic testing to identify if they carry the same mutation. 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 mutation, 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 mutation, 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.

2.4 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 at 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 unrecognized 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, mutation prevalence might be higher than clinical prevalence, as was the case with HCM (Section 1.5). Hall et al. (2018) estimated the population prevalence of ARVC-related mutations 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 mutations associated with ARVC, a prevalence of 1/200 (Lahtinen et al. 2011). In Section 6.1, we see how this might significantly reduce adverse selection costs.

2.5 Penetrance

Quarta et al. (2011) estimate the penetrance $F(x)$ (see Section 1.2) 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 2.6), this study did not distinguish gender.

2.6 Mortality

We present estimates of the annual hazard rate of ARVC-related mortality in Tables 1, 2, and 3, 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 $E^c_x$ among a group of $n_x$ observed individuals labelled with the age $x$ (see Macdonald et al. (2018)). The age label $x$ refers to a range of ages within which the assumed hazard rate is assumed to be constant.

(a) Table 1 summarizes studies of ARVC regardless of ICD treatment.
(b) Table 2 compares the mortality hazards of probands and their relatives, regardless of ICD treatment.
(c) Table 3 summarizes studies of ARVC after ICD treatment.

The average age at entry into the studies in Tables 1, 2, and 3 was between the third and fourth decades of life. The studies predominantly included men.

2.6.1 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 3, results from a study reporting a single death). Corrado et al. (2017) 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 centers, which predominantly included high-risk patients. Recent studies of community-based patient cohorts have shown that the long-term
Table 1: 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. 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. $E_x^c$: 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.

<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>$E_x^c$</th>
<th>$\mu_x$</th>
<th>Reference</th>
</tr>
</thead>
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<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>
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<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)*</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)**</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)*</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)§</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)§κ</td>
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<tr>
<td>n/a</td>
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<td>n/a</td>
<td>n/a</td>
<td>4</td>
<td>425.00</td>
<td>0.94</td>
<td>Quarta et al. (2011)§κ</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>
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<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)#</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)†</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)†</td>
</tr>
</tbody>
</table>

* $n_x = 132$ 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.
† Mean follow-up time (unreported) was assumed to be as same as median follow-up time.
§ 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.
κ 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 2: 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 Groeneweg et al. (2015). Probable mutation carriers represent first degree-relatives of probands with unknown mutation(s). Please see the headings in Table 1.

<table>
<thead>
<tr>
<th>Family Member</th>
<th>Mutation 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>
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<tbody>
<tr>
<td>Proband</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>
<td></td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td></td>
<td>23</td>
<td>n/a</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>n/a</td>
<td>1.28</td>
</tr>
<tr>
<td>Relative</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>
<td></td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td></td>
<td>24</td>
<td>n/a</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>n/a</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>9</td>
<td>0</td>
<td>459</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td></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>

* For $n_x = 439, 409, 153$, 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 $E^c_x = 3512, 1636, 459$, in each group that also assumed to be same for the $n_x = 416, 385, 152$ alive individuals at entry in these groups.

Table 3: Annual hazard rate of ARVC-related mortality ($\mu_x$) based on the clinical cohorts who had an ICD treatment were followed-up. Please see the headings in Table 1. This table is based on Basso et al. (2012), Table 4 and Calkins et al. (2017), Table 2.

<table>
<thead>
<tr>
<th>Reference</th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Link et al. (1997)</td>
<td>31 ± 19</td>
<td>12</td>
<td>58</td>
<td>1</td>
<td>21.96</td>
<td>4.56</td>
</tr>
<tr>
<td>Tavernier et al. (2001)</td>
<td>36 ± 18</td>
<td>9</td>
<td>89</td>
<td>0</td>
<td>24.03</td>
<td>0.00</td>
</tr>
<tr>
<td>Corrado et al. (2003)*</td>
<td>40 ± 15</td>
<td>132</td>
<td>70</td>
<td>3</td>
<td>435.60</td>
<td>0.69</td>
</tr>
<tr>
<td>Wichter et al. (2004)</td>
<td>43 ± 16</td>
<td>60</td>
<td>82</td>
<td>4</td>
<td>396.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Roguin et al. (2004)</td>
<td>36 ± 13</td>
<td>42</td>
<td>52</td>
<td>0</td>
<td>147.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Hodgkinson et al. (2005)¶</td>
<td>35.9</td>
<td>48</td>
<td>63</td>
<td>0</td>
<td>124.80</td>
<td>0.00</td>
</tr>
<tr>
<td>Piccini et al. (2005)κ</td>
<td>36 ± 14</td>
<td>67</td>
<td>52</td>
<td>2</td>
<td>294.80</td>
<td>0.68</td>
</tr>
<tr>
<td>Corrado et al. (2010)</td>
<td>35.6 ± 18</td>
<td>106</td>
<td>67</td>
<td>0</td>
<td>511.98</td>
<td>0.00</td>
</tr>
<tr>
<td>Bhousale et al. (2011)†</td>
<td>31.9 ± 11.9</td>
<td>84</td>
<td>46</td>
<td>1</td>
<td>397.32</td>
<td>0.25</td>
</tr>
<tr>
<td>Schuler et al. (2012)¶</td>
<td>n/a</td>
<td>26</td>
<td>81</td>
<td>2</td>
<td>278.20</td>
<td>0.72</td>
</tr>
<tr>
<td>Link et al. (2014)</td>
<td>40 ± 14</td>
<td>108</td>
<td>60</td>
<td>0</td>
<td>356.40</td>
<td>0.00</td>
</tr>
<tr>
<td>Orgeron et al. (2017)†</td>
<td>33.6 ± 13.9</td>
<td>312</td>
<td>52</td>
<td>3</td>
<td>2745.60</td>
<td>0.11</td>
</tr>
</tbody>
</table>

* Heart transplantation (HT) was evaluated as an endpoint.
† Mean follow-up time (unreported) was assumed to be as same as median follow-up time.
κ Of $n_x = 67$, 12 were noted to be with ‘probable ARVC’.
† An ICD intervention and heart transplant were evaluated as endpoints.
outcome for treated index patients and family members is favorable (annual mortality, <1%)."

(This is consistent with the description of how epidemiology evolves given in Section 1.3.)

Haçarız (2020) noted that the estimated mortality hazard of HCM reduced from 3–6% in 1958, until by the 1990s, a hazard of about 1% was widely cited. Based on more recent studies he estimated a mortality hazard of 0.55%. The reduction was due to reducing selection bias, modern diagnosis and treatment, and the exclusion of non-fatal endpoints from the mortality hazard (Section 2.1.1). The first two factors are also relevant for ARVC, but the last seems not to be. Some studies (see Tables 1 and 3) do include as endpoints non-fatal ARVC events such as heart transplantation (HT), which means that mortality hazards estimated from these studies are overstated. Since this is relatively minor and conservative for our purposes we make no attempt to correct for it.

2.6.2 ICD Treatment

Tables 1 and 2 state the proportion of subjects who had ICD treatment, when known. Table 3 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.

2.6.3 Relatives of Probands

There is some evidence that at-risk relatives of probands (those who carry an identified mutation) might have lower ARVC-related mortality, which might be explained by them receiving early clinical care. See Nava et al. (2000) in Table 1 and Groeneweg et al. (2015) in Table 2. 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 2 shows that the annual mortality hazard of ARVC in probands might be about twice that of their relatives.

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. We suppose that $i$ is a label representing a sub-population, related to genotype as described in Section 3.2. The model represents events in a life history, as follows:

(a) At any time, buying life insurance.
(b) Onset of the underlying condition (of ARVC).
(c) Clinical diagnosis after onset.
(d) Being fitted with an ICD after clinical diagnosis.
(e) Having a genetic test for an ARVC-related variant.
(f) Suffering a fatal ARVC-related event before or after an ICD implantation.
(g) Death from any other cause.

Haçarız (2020) and Haçarız et al. (2020) defined a similar model for HCM, though simpler in that onset and clinical diagnosis of the underlying condition were not represented as events.
Figure 1: A mathematical model of adverse selection in ARVC for a person in the ith of several sub-populations defined by ARVC genotype in a life insurance market. In $\mu_{i0}^{02}$ and $\mu_{i46}^{46}$, $z$ refers to duration in state $i0$ and state $i4$ since (if) a proband appeared in family. ICD: Implantable cardioverter-defibrillator.
The key assumption is that the model represents the life history of a single individual in a nuclear family, but we model all the members of a 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 by insurers, if allowed, in setting premium rates, and by individuals, in deciding whether to take a genetic test, and whether to buy life insurance, and if so the sum insured.

The following is a brief outline of the main model features. Except for the state space and transitions, the model features are the same as in Haçarız et al. (2020), and we refer to that for a detailed account.

3.2 Sub-populations

There are five sub-populations, labelled $i = 0, 1, 2, 3, 4$. Sub-population 0 contains individuals who do not carry an ARVC-related mutation. Sub-populations 2 and 4 contain individuals who carry known and unknown ARVC-related variants, respectively. Sub-populations 1 and 3 are populated dynamically, through the formation of families, 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. We assume that everyone in sub-populations 2 and 4 acquires a spouse who does not carry an ARVC-related variant. That is, they marry someone of the opposite sex from sub-population 0. That person is moved from sub-population 0 to sub-population 1 or 3, depending on whether their spouse is in sub-population 2 or 4, respectively.

(c) At calendar time 30, children are born in families in which both spouses are alive. The number of children is random, with a Poisson($\lambda$) distribution (so the number could be zero). Children are male with probability $1/2$. Children born in families in which either spouse is in sub-populations 2 or 4 inherit the ARVC-related variant with probability $1/2$, according to Mendel’s law, and are allocated to sub-population 1, 2, 3 or 4 accordingly. Our default assumption for mean family size is $\lambda = 1.8$, which is roughly correct for both the UK and USA.

Therefore, individuals in sub-populations 1 and 3 are members of families in which an ARVC-related mutation is present, but they do not themselves carry it. Individuals in sub-populations 0, 1 and 3 face identical biological risks, but both they and insurers may make decisions depending on their family history.

3.3 Probands and Family History

At calendar time 0, no-one has ARVC. A person may become the proband within a family, 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 in Section 2.3, this event initiates CGT in the family, and it bestows a family history of ARVC upon every surviving family member.
3.4 The Cascade Genetic Testing Model

In principle, as soon as a proband appears in a family genetic testing becomes a possibility. First, the proband will be tested for known mutations. If one is identified, counselling and genetic testing will be offered to all the proband’s first-degree relatives. Haçař (2020) considered take-up rates of testing in HCM and (in the absence of much empirical data) other inherited disorders such as breast and colon cancer. Based on that, he assumed that for one year after a proband has appeared, there is a constant intensity of transferring from an untested to a tested state, such that the probability of being tested is 1/2, represented by a testing hazard rate of 0.6931472. In practice, further assumptions were needed to deal with less common possibilities, such as a proband appearing when children were very young. We refer to Haçař (2020) for details, and adopt the same assumptions as there.

In families in which an unknown mutation 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 Haçař et al. (2020) noted that an effective proxy is to increase the value of $\lambda$, since everyone offered testing under CGT is a mutation carrier with probability 1/2.

3.5 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 mutation. 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.

3.6 Information: Insurance Purchasing

At any time, each living 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 $\zeta^n$.

3.7 A Measure of Adverse Selection Costs

We use the same measure of adverse selection costs as in Haçariz et al. (2020), 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. 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 loss and premium income in population $X$ change to $L^*_X$ and $P^*_X$, and our measure is then:

$$
\frac{E[L^*_X + L_Y]}{E[P^*_X + P_Y]}.
$$

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 (2020) and Haçariz et al. (2020) for details.

4. Results: Adverse Selection Costs

4.1 Baseline Scenarios

4.1.1 Mutation Prevalence

Based on Section 2.4, we assume the mutation prevalence to be $1/1000$. Although this in fact is based on the clinical prevalence of 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 6.1. Based on Section 2.2, we also assume 70% of mutations to be ‘known’ and 30% ‘unknown’.

4.1.2 Mutation Penetrance

We conservatively estimate the penetrance of clinical ARVC at age $x$ ($10 \leq x \leq 60$) to be $F(x) = 0.01x$, relying on the reported data in Quarta et al. (2011), see Section 2.5. 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) assumed annual mortality \( (q_x) \) of 2.3% per year. In view of the discussion in Section 2.6, this seems excessive, and possibly based on outdated epidemiology. The comment by Corrado et al. (2017), quoted in Section 2.6.1, suggests that an annual hazard of less than 1% would be appropriate, and comparison of Tables 1 and 3 suggests that allowance should be made for implanting an ICD. Table 2 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.

We estimate ARVC-related mortality after ICD treatment by aggregating the deaths and exposures of all the studies listed in Table 3, resulting in an annual hazard rate of 0.28%.

4.1.4 Population Mortality

The population mortality rates 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. (2020), and earlier authors, 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 lapsation is significant. We then superimpose higher annual purchase rates, of 0.10 or 0.25, depending dynamically on the information class (Section 3.6) to represent moderate or severe adverse selection, respectively. Specifically, persons in information classes \( \zeta^{50} \) and \( \zeta^{100} \) 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 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 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 follow-up of 1432
person-years. Possibly, these study populations were more heterogeneous than those
in (a).

As a result, 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%.

4.3 Comparison With Howard (2014)

Based on the dollar costs attributed to ARVC in Howard (2014) (see Section 1.1),
namely $111,141,682 out of a total adverse selection cost of $405,455,952, added to esti-
minated 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.

4.4 Baseline Adverse Selection Costs

We summarise the baseline assumptions in Table 4, and present the premium increases
under the baseline adverse selection scenarios in Table 5. 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.

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 mutation carriers before the assumed
reproductive age of 30.

5. Factors Amplifying Adverse Selection Costs

5.1 Family History Disallowed in Underwriting

We noted, in Section 4.4, 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. (2020)).
Table 4: Baseline assumptions for the model parameters.

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of non-ARVC mutations in the general population at age 20</td>
<td>0.999</td>
<td>Section 4.1.1</td>
</tr>
<tr>
<td>Prevalence of ARVC mutations in the general population at age 20</td>
<td>0.001</td>
<td>Section 4.1.1</td>
</tr>
<tr>
<td>Prevalence of known mutations in the ARVC population at birth</td>
<td>70%</td>
<td>Section 4.1.1</td>
</tr>
<tr>
<td>Prevalence of unknown mutations in the ARVC population at birth</td>
<td>30%</td>
<td>Section 4.1.1</td>
</tr>
<tr>
<td>Hazard rate of penetrance of ARVC per annum at ages 10–60</td>
<td>$\mu^O_x$</td>
<td>Section 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*</td>
<td>Section 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*</td>
<td>Section 4.1.5</td>
</tr>
<tr>
<td>Proportion of individuals having an ICD treatment at all ages</td>
<td>0%§</td>
<td>Section 4.2</td>
</tr>
<tr>
<td>Hazard rate of fatal ARVC before an ICD treatment per annum for all ages</td>
<td>1%</td>
<td>Section 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>Section 4.1.3</td>
</tr>
<tr>
<td>Hazard rate of all other death per annum for all ages</td>
<td>$\mu^A_x$</td>
<td>Section 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>$\mu^{T}_{x,1}$</td>
<td>Section 3.4</td>
</tr>
<tr>
<td>Hazard rate of normal insurance purchase per annum at ages 20–60</td>
<td>5%</td>
<td>Section 4.1.6</td>
</tr>
<tr>
<td>Normal sum assured</td>
<td>£1</td>
<td>Section 4.1.6</td>
</tr>
<tr>
<td>Force of interest per annum</td>
<td>5%</td>
<td>Section 4.1.6</td>
</tr>
</tbody>
</table>

* $\mu^O_x = F'(x)(1 - F(x))^{-1}$ where $F(x) = 0.01x$, estimated penetrance of clinical ARVC at age $x$.

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

§ This represents a proportion of annual rate of clinically diagnosed individuals.

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

$\mu^{T}_{x,1} = 0.6931472$, which represents 50% of untested individuals taking up genetic testing in one year.

Table 5: Percentage increases in premiums due to baseline adverse selection scenarios (Section 4.4 and Table 4). The 95% quantile intervals (QI) are in respect of the Monte-Carlo estimation of mean EPVs of cashflows in the ARVC families (see Section 3.7).

<table>
<thead>
<tr>
<th>Adverse 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>
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 $\zeta^{50}$ and $\zeta^{100}$ under ‘mild’ and ‘severe’ adverse selection is twice (0.02) and twenty-five times (0.25) the normal purchase rate, respectively. We present the results in Table 6, “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 $\zeta^{50}$ and $\zeta^{100}$ increase their purchases of insurance, but they still choose the ‘normal’ sum insured. We consider here higher sums insured for these classes. Following the notation in Section 3.7 and Haçarız et al. (2020), $L^*_X$ is decomposed into two parts:

(a) $L_X^{*(1)}$, representing those in population $X$ who purchase higher sums insured; and
(b) $L_X^{*(2)}$, representing those in population $X$ 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:

$$\frac{E[nL_X^{*(1)} + L_X^{*(2)} + L_Y]}{E[nP_X^{*(1)} + P_X^{*(2)} + P_Y]}.$$ (2)

Table 6, “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 6, “Proportion Tested”, presents the premium increases if 99% of ‘untested’ individuals (instead of 50%, see Section 3.4) accept testing within a year of a proband appearing in the family. This corresponds to a testing hazard rate of 4.60517.

(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.

(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 3.5).

(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 mutation carrier with probability 1/2. We present the results in Table 6, “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 6, “ARVC Mortality”. The premium increases are about twice those with the mortality hazard rate of 1%.

5.6 Rate of Clinical Diagnosis

Haçarız (2020) and Haçarız et al. (2020) 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 6, “Clinical Diagnosis”, presents the premium increases under the baseline scenario of adverse selection (see Section 4.4), 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 6, “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 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 7 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 $\zeta^{50}$ and $\zeta^{100}$ purchase ten times the normal sum insured. With an ARVC-related
Table 6: Mean percentage increases in premiums (95% QIs omitted) due to changing parameters (resulting an amplification in adverse selection costs) in baseline adverse selection scenarios (Section 5). ‘None’ refers to the ‘normal’ purchase intensity.

<table>
<thead>
<tr>
<th>Section</th>
<th>Varied Parameter</th>
<th>Family History Disallowed Adverse Selection</th>
<th>Family History Allowed Adverse Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>Mild</td>
</tr>
<tr>
<td>5.2</td>
<td>Purchase Intensity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>0.0000</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>0.0000</td>
<td>0.0120</td>
</tr>
<tr>
<td>5.3</td>
<td>Sum Insured¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 ×</td>
<td>0.0000</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>2 ×</td>
<td>0.0160</td>
<td>0.0313</td>
</tr>
<tr>
<td></td>
<td>4 ×</td>
<td>0.0480</td>
<td>0.0785</td>
</tr>
<tr>
<td></td>
<td>10 ×</td>
<td>0.1438</td>
<td>0.2197</td>
</tr>
<tr>
<td>5.4</td>
<td>Proportion Tested§</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>0.0000</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>99%</td>
<td>0.0000</td>
<td>0.0076</td>
</tr>
<tr>
<td>5.4</td>
<td>CGT Extension#</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>λ = 1.8</td>
<td>0.0000</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>λ = 3.0</td>
<td>0.0000</td>
<td>0.0103</td>
</tr>
<tr>
<td></td>
<td>λ = 5.0</td>
<td>0.0000</td>
<td>0.0135</td>
</tr>
<tr>
<td></td>
<td>λ = 7.0</td>
<td>0.0000</td>
<td>0.0160</td>
</tr>
<tr>
<td>5.5</td>
<td>ARVC Mortality†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>0.0000</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>2.3%</td>
<td>0.0000</td>
<td>0.0146</td>
</tr>
<tr>
<td>5.6</td>
<td>Clinical Diagnosis‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.0000</td>
<td>0.0053</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>0.0000</td>
<td>0.0070</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>0.0000</td>
<td>0.0077</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>0.0000</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>0.30</td>
<td>0.0000</td>
<td>0.0074</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.0000</td>
<td>0.0071</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>0.0000</td>
<td>0.0070</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>0.0000</td>
<td>0.0067</td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>0.0000</td>
<td>0.0066</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
<td>0.0000</td>
<td>0.0065</td>
</tr>
</tbody>
</table>

* Annual purchase intensities in a large and smaller life insurance markets, respectively.
¶ Increased sums insured taken out by adverse selectors.
§ A higher rate of uptake of genetic testing, with approximately 99% acceptance instead of 50%.
# Extending cascade genetic testing (CGT) as a proxy beyond the first generation by increased values of \( \lambda \), the mean number of children.
† ARVC-related annual mortality hazard rates.
‡ Annual hazard rate of clinical diagnosis of those who have suffered onset of ARVC.
Table 7: Percentage increases in premiums caused by the increased sum insured (10\times of normal) in a smaller life insurance market (the ‘normal’ insurance purchase intensity of 0.01) under ‘severe’ adverse selection (Section 5.7).

<table>
<thead>
<tr>
<th>ARVC Mortality†</th>
<th>Mean Premium Increase and 95% QI</th>
<th>Family History Disallowed</th>
<th>Family History Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>† ARVC-related annual mortality hazard rates.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td># The mean number of children in which $\lambda = 7.0$ represents extensive cascade genetic testing.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>1.8 1.0327 (0.7814 , 1.3209) 0.3240 (0.0767 , 0.6075)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>7.0 2.1256 (1.8774 , 2.3757) 0.6463 (0.4043 , 0.9015)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td>7.0 4.1815 (3.8720 , 4.4976) 1.2160 (0.9145 , 1.5315)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. FACTORS DIMINISHING ADVERSE SELECTION COSTS

6.1 Different Mutation Prevalences

Based on the opinion of Corrado et al. (2017a) (see Section 2.4) we will assume a lower mutation prevalence of 1/5000. Alternatively, based on the results of Lahtinen et al. (2011) (see Section 2.4) we will assume a higher mutation prevalence of known mutations of 1/200, which would increase to at least 1/140 \approx 0.7% when non-desmosomal and unknown gene mutation carriers (Section 4.1.1) were included.

The higher prevalence of 0.7% models ‘silent’ ARVC mutations 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 8, “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.

6.2 ICD Treatment

A noteworthy distinction between this study and Haçarz et al. (2020) is that an effective treatment for ARVC is available, namely the implantation of an ICD. The large reductions in mortality were summarized in the studies shown in Table 3.

We model ICD implantation in the light of Section 4.2, which states that a proportion of clinically diagnosed individuals will immediately receive an ICD, and others never do. The proportions we assume are 0%, 25%, 50%, 75% and 100%. We present the results
in Table 8, “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.

6.3 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 Section 1.3. (See Hodge (2002) and the references therein for the large literature on this subject. See also Lemaire et al. (2000), Macdonald et al. (2003), and Haçarız et al. (2020) for actuarial perspectives of these biases.) 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 these disorders are rare. However, as the epidemiology evolves over time, we may partially overcome these biases, and 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 8, “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.

6.4 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 mutation 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 8, “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.

7. Conclusions

We modelled premium increases arising from adverse selection caused by life insurers being barred from adverse genetic test results for ARVC-related mutations. 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), Haçarız (2020) and Haçarız et al. (2020).

(b) Premium increases seem to be smaller than those found for HCM in comparable scenarios (Haçarız (2020) and Haçarız et al. (2020)). Howard (2014) found the opposite.
Table 8: Mean percentage increases in premiums (note that 95% QIs omitted) due to changing parameters (resulting a diminish in adverse selection costs) in baseline adverse selection scenarios (Section 6). ‘None’ refers to the ‘normal’ purchase intensity.

<table>
<thead>
<tr>
<th>Section</th>
<th>Varied Parameter</th>
<th>Biological/Behavioural</th>
<th>Purchase Intensity</th>
<th>Sum Insured</th>
<th>Family History Disallowed</th>
<th>Family History Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Prevalence*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0076 0.0164</td>
</tr>
<tr>
<td></td>
<td>0.02%</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0015 0.0032</td>
</tr>
<tr>
<td></td>
<td>0.7%</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0010 0.0021</td>
</tr>
<tr>
<td>6.2</td>
<td>ICD Treatment¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 0% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0076 0.0164</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 25% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0069 0.0145</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 50% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0058 0.0124</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 75% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0048 0.0103</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 100% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0038 0.0082</td>
</tr>
<tr>
<td>6.3</td>
<td>Selection Bias§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 0% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>-0.0697 -0.0620 -0.0533</td>
<td>-0.0710 -0.0739 -0.0750</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 50% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>-0.0855 -0.0797 -0.0731</td>
<td>-0.0871 -0.0920 -0.0953</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 100% )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>-0.1019 -0.0982 -0.0937</td>
<td>-0.1038 -0.1109 -0.1165</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 0% )</td>
<td>0.01</td>
<td>1 ×</td>
<td></td>
<td>-0.0595 -0.0475 0.0327</td>
<td>-0.0607 -0.0686 -0.0950</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 50% )</td>
<td>0.01</td>
<td>1 ×</td>
<td></td>
<td>-0.0741 -0.0645 -0.0035</td>
<td>-0.0755 -0.0860 -0.1329</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 100% )</td>
<td>0.01</td>
<td>1 ×</td>
<td></td>
<td>-0.0880 -0.0815 -0.0406</td>
<td>-0.0897 -0.1035 -0.1716</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 0% )</td>
<td>0.01</td>
<td>10 ×</td>
<td></td>
<td>0.0688 0.1880 0.9724</td>
<td>-0.1535 -0.2310 -0.4836</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 50% )</td>
<td>0.01</td>
<td>10 ×</td>
<td></td>
<td>0.0249 0.1192 0.7162</td>
<td>-0.1996 -0.3035 -0.7523</td>
</tr>
<tr>
<td></td>
<td>( p_{ICD} = 100% )</td>
<td>0.01</td>
<td>10 ×</td>
<td></td>
<td>-0.0190 0.0456 0.4454</td>
<td>-0.2463 -0.3820 -1.0349</td>
</tr>
<tr>
<td>6.4</td>
<td>Information Class†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \zeta^{50} &amp; \zeta^{100} )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0076 0.0164</td>
</tr>
<tr>
<td></td>
<td>( \zeta^{100} )</td>
<td>0.05</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0027 0.0056</td>
</tr>
<tr>
<td></td>
<td>( \zeta^{50} &amp; \zeta^{100} )</td>
<td>0.01</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0120 0.0923</td>
</tr>
<tr>
<td></td>
<td>( \zeta^{100} )</td>
<td>0.01</td>
<td>1 ×</td>
<td></td>
<td>0.0000</td>
<td>0.0043 0.0328</td>
</tr>
<tr>
<td></td>
<td>( \zeta^{50} &amp; \zeta^{100} )</td>
<td>0.01</td>
<td>10 ×</td>
<td></td>
<td>0.1284 0.2477 1.0327</td>
<td>0.0202 0.0432 0.3240</td>
</tr>
<tr>
<td></td>
<td>( \zeta^{100} )</td>
<td>0.01</td>
<td>10 ×</td>
<td></td>
<td>0.0460 0.0891 0.3724</td>
<td>0.0255 0.0499 0.2306</td>
</tr>
</tbody>
</table>

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

† \( p_{ICD} \) represents a constant proportion of clinically diagnosed individuals immediately having an ICD implantation.

‡ 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.
(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 (see Table 8, “Selection Bias”). 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.

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