

NATIONAL UNIVERSITY OF IRELAND, GALWAY

DOCTORAL THESIS

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**Medicalisation in Ireland – A Mixed Methods  
Analysis using the Case of Statins for Primary  
Prevention of Cardiovascular Disease**

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*A thesis submitted in application for the degree of Doctor of Philosophy  
to the J.E. Cairnes School of Business and Economics*

*by*

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# Declaration of Authorship

I, Paula Byrne, declare that this thesis, submitted to the National University of Ireland, Galway for the degree of Doctor of Philosophy (Ph.D.) has not been previously submitted as an exercise for a degree at this or any other University. All research herein is entirely my own. Chapters 3 to 7 have been published in, or submitted to, academic journals for publication. As these papers included supervisors' inputs, as well as inputs from collaborators, I specify here my own contributions and leadership, as well as the contributions of my co-authors, to each discrete piece of work:

- Chapter 3: Paula Byrne (PB) was the lead researcher and involved in the design, implementation, analysis and reporting of the study. John Cullinan (JC), Catriona Murphy and Susan M Smith (SS) provided contributions to the conception, design, analysis and reporting of the work.
- Chapter 4: PB was the lead researcher and involved in the design, implementation, analysis and reporting of the overview. PB conducted the initial search for systematic reviews. PB and Amelia Smith (AS) undertook title and abstract screening, full text screening, extraction of data and quality assessment. SS arbitrated any disagreements between PB and AS on inclusion and quality assessment of reviews. JC and SS provided contributions to the conception, design, analysis and reporting of the work.
- Chapter 5: PB was the lead researcher and involved in the design, implementation, analysis and reporting of the study. JC, Paddy Gillespie (PG) and Rafael Perera (RP) provided advice and feedback on analysis on costs, patient preferences and modelling. JC, PG, RP and SS provided contributions to the conception, design, analysis and reporting of the work.
- Chapter 6: PB was the lead researcher and involved in the design, implementation, analysis and reporting of the study with contributions from supervisor Órla O'Donovan (OOD) on the conceptualisation, theoretical underpinnings and analysis of the literature. JC and SS provided contributions to the conception and reporting of the work.
- Chapter 7: PB was the lead researcher and involved in the design, implementation, analysis and reporting of the study with contributions from OOD on the conceptualisation, theoretical underpinnings and analysis of the interviews. JC and SS provided contributions to the conception and reporting of the work.

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# List of Abbreviations

ACC	American College of Cardiologists
AHA	American Heart Association
AMA	American Medical Association
AR	Absolute Risk
ARR	Absolute Risk Reduction
BMJ	The British Medical Journal
CAPI	Computer Aided Personal Interview
CARE	Cholesterol and Related Events Trial
CEA	Cost Effectiveness Analysis
CHD	Coronary Heart Disease
CI	Confidence Interval
COREQ	COnsolidated criteria for REporting Qualitative research
CTT	Cholesterol Treatment Trialists Collaboration
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DTC	Direct to Consumer
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GMS	General Medical Services
GP	General Practitioner/General Practice
HMG-CoA	3-hydroxy-3-methylglutaryl co-enzyme A
HSE	Health Service Executive
ICA	Irish Countrywomen's Association
IHD	Ischaemic Heart Disease
IPD	Individual Patient Data
IPS	Irish Prison Service
LRC-CPPT	The Lipid Research Clinics Coronary Primary Prevention Trial

LDL	Low-density Lipoprotein
mg/dL	Milligrams per Deciliter
MI	Myocardial Infarction
mmol/L	Millimoles per Litre
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Blood and Lung Institute
NNT	Number-needed-to-treat
OR	Odds Ratio
PAC	Potential Artherosclerotic Conditions
PCRS	Primary Care Reimbursement Service
PCSK9	Proprotein convertase subtilisin/kexin type 9
PRISMA-IPD	Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data
R-AMSTAR	Revised Assessment of Multiple Systematic Reviews
RCT	Randomised Control Trials
RR	Relative Risk
4S	Scandinavian Simvastatin Survival Study
SCORE	Systematic COronary Risk Evaluation
SDM	Shared Decision Making
SR	Systematic Review
TC	Total Cholesterol
TILDA	The Irish Longitudinal Study on Ageing
WestREN	Western Research and Education Network
WHO	World Health Organization
WPR	What's the Problem Represented to Be?

# Glossary

Expanded disease definitions	Expansion of official disease or risk categories, or creating new conditions or promoting more frequent diagnosis of recognised conditions without net benefit to patients or citizens (Carter et al., 2015).
Medicalisation	Medicalisation is conceptualised as a process whereby non-medical problems become defined and treated as medical problems. The term itself does not imply a value judgement as to whether this change is good or bad, but merely notes that ‘the problems have moved into medical jurisdiction’ (Conrad et al., 2010).
Overdiagnosis	An asymptomatic person is diagnosed with a condition; that diagnosis does not produce a net benefit for that person (Carter et al., 2015).
Primary prevention	People with risk factors for cardiovascular disease who have not yet developed clinically manifest disease (World Health Organization, 2017).
Secondary prevention	People with established coronary heart disease, cerebrovascular disease, or peripheral vascular disease (World Health Organization, 2017).
Shared decision making	An approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences (Elwyn et al., 2010).

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# Dedication

For my parents, Paddy and Kay, my husband Henry and our children Emmet, Tom and Eva May.

# Abstract

Statins are a class of drugs that lower blood cholesterol levels and were originally used to prevent further recurrences in those with a history of cardiovascular disease (CVD). Over time, their use has been extended to those with no prior history but who may be at risk of CVD in the future, referred to as primary prevention. The increase in the proportion of people taking statins for primary prevention has raised concern about the medicating of asymptomatic people, a process described as medicalisation. The aim of this thesis is to explore the increased use of statins within the context of primary prevention of CVD and to consider whether or not this constitutes an appropriate use of this medicine both from the perspective of the individual patient and of society.

In order to establish the proportion of statin users and reasons for statin use, an analysis of data from The Irish Longitudinal Study on Ageing (TILDA) was undertaken. Almost one third of over-50s were using statins and, of those, almost two-thirds were doing so for primary prevention of CVD. However, while just over a half of men who took statins did so for primary prevention, almost three quarters of women did likewise. This analysis of TILDA data also suggests that there may be an overemphasis on high cholesterol as a reason to prescribe, rather than prescribing based on a person's overall risk assessment. Given the common use of statins for primary prevention, an overview of systematic reviews of exclusively primary prevention data regarding the effectiveness of statins for prevention of CVD was then conducted, finding mixed and limited evidence on the effectiveness of statins in primary prevention populations, particularly in women.

Changes in the recommendations of clinical guidelines have been identified as a driver of the medicalisation process in general, and changes in the clinical guidelines for CVD prevention since 1987 have resulted in almost 62% of over-50s becoming eligible for statin therapy by 2016. This has significant implications for State spending on statins and also implies that many low-risk people have become eligible for statin therapy. As a result, many statin users may not achieve risk reductions needed to justify taking a daily medicine. Another driver of medicalisation is how people themselves, both doctors and patients, subscribe to particular ways of understanding primary prevention of CVD. By exploring these issues through analyses of semi-structured interviews, it was found that rather than high cholesterol being seen as one of several risk factors that may contribute to heart disease, it tended to be reified and evaluated as a current problem. Statins were represented as a necessary medicine that many patients, and doctors, felt they did not have a choice about taking or prescribing. Taking statins for life is a common biomedically sanctioned experience in Ireland, indicating that this has been a site of medicalisation.

The fundamental question that motivated the analyses in this thesis is whether the benefits of statins outweigh the costs, opportunity costs, or harms to society and to the

individual patient? Low-value care has been defined as healthcare that offers little clinical benefit but has the potential to cause harm and I argue that for many patients in primary prevention, and for the State reimbursing those patients, statin use may be an example of low-value care and, in some cases, represent a waste of healthcare resources. However, the boundaries between appropriate use, overuse and low-value care are difficult to delineate. Therefore, to conclude, I argue that the prescription, use and reimbursement of statins in primary prevention warrants more careful consideration incorporating patient preferences and numbers-needed-to-treat, and that the concept of overuse and low-value care should become integral to policy making.

# 1 Introduction

This thesis presents a mixed methods analysis of the medicalisation process using the case of statins for primary prevention of cardiovascular disease as an exemplar. To begin, the context and motivation for this research are presented in Section 1.1 of this chapter. Section 1.2 then describes the genesis of statins and their mode of action, followed by an outline of the development of clinical guidelines that established statins as central to the prevention of cardiovascular disease. The relevant cardiovascular health policy in Ireland is also considered in this section, along with a summary of Irish and international trends in statin use. Because the use of statins, particularly in primary prevention, has attracted controversy from the very beginning of statin use, some of these often-polarised debates are described in Section 1.3. Following this, in Section 1.4, the research aims and objectives of this thesis are presented. Section 1.5 then provides an overview of the methods and data used throughout to address these aims and objectives. The chapter concludes with a summary outline of the thesis in Section 1.6.

## 1.1 Context and Motivation

The broad context for this research is the marked increase in the use of pharmaceutical drugs in many countries over the last decades. This has significant implications for resource allocation in health and health care, and for contemporary meanings and experiences of patienthood. Across OECD countries, pharmaceutical spending reached over US\$800 billion in 2013 (Belloni, 2016) and the consumption of medicine continues to rise. Debate has ensued as to whether this increase is justified in terms of patient or population health outcomes (Heath, 2013, Le Fanu, 2018), whether it constitutes overuse of medicine (Moynihan et al., 2012, Grady and Redberg, 2010, Carter et al., 2015), and whether it threatens the sustainability of health care systems (Getz et al., 2004, Glasziou, 2018, Connors, 2017a). In Ireland, there has been a substantial increase in spending on pharmaceuticals, both in absolute terms and in per capita terms compared to other OECD countries (Brick et al., 2013, p.131). In addition, Ireland ranks as one of the highest countries in terms of units of drugs dispensed per capita in a comparison of sixteen European countries (Connors, 2017a, p.12).

This increased utilisation of drugs has been linked to the process of ‘medicalisation’. Medicalisation occurs when non-medical problems come to be defined as medical problems and are treated by medical solutions. Many advances in healthcare have resulted from this process, alleviating the suffering of millions. For example, the advances in scientific understanding of hypertension by Irish-Indian physician Frederick Akbar Mahomed in the late nineteenth century, along with the subsequent discoveries of the mercury sphygmomanometer and effective pharmaceutical treatments (Saklayen and Deshpande, 2016), saved thousands of people from certain death per year, and allowed them to live longer and healthier lives. However, medicalisation can also lead to overuse of medicine and the widespread use of interventions that provide little benefit for many recipients. For example, the lowering of thresholds of what constitutes ‘high’ blood pressure has resulted in large increases in the number of people labelled as hypertensive (Maturo, 2012). The opportunity cost of such resource allocation is the restriction of spending on more beneficial health-care interventions or on improvements in health-related social and economic conditions.

As a result of such negative impacts, the World Health Organization (WHO) has recognised the need to identify the overuse of medicine and in 1985 coined the phrase ‘rational use of medicine’ whereby:

Patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community (Bigdeli et al., 2014).

As implied by this WHO statement, distinguishing medicalisation that is harmful and that can be considered overuse is complex, requiring analysis of specific diagnostic or therapeutic categories and of the specific needs and preferences of the individual patient. More recently, the WHO has preferred the use of the term ‘appropriate use’ of medicine to the term ‘rational use’. This is because the rational use of medicine may in fact still be inappropriate, as inappropriate use includes overuse, underuse, or inefficient use of medicines, including, for example, using antibiotics for viral infections or non-adherence to chronic treatment regimens (Bigdeli et al., 2014, p.23). It is important to understand, too, that medicines are no longer prescribed only to treat the sick, but can also be used to reduce the risk of future illness (Busfield, 2015). In addition, a simplistic view that a

medicine is either effective or not effective, runs the risk of overlooking consideration of the risk-benefit equation; does the benefit of taking the medicine outweigh the harm, the cost and the disutility of taking a medicine from a societal or individual patient's perspective? Shared decision-making (SDM), a concept that considers the right of a person to self-determination, may be one way of establishing the risk-benefit equation from the perspective of the individual. SDM has been defined as 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences' (Elwyn et al., 2012). From a societal perspective, techniques such as cost-effectiveness analysis (CEA) can be useful to determine the net benefit of medicalisation. Both SDM and CEA are considered at various points throughout the thesis and in the discussion in Chapter 8.

In this context, this thesis responds to calls for the examination of the appropriate use of drugs and the value of medicalisation in the treatment of specific conditions and contexts (Busfield, 2015, Carter et al., 2015). Statins were chosen as an exemplar of the difficulty in establishing the boundaries of appropriate use and overuse, as well as the process of medicalisation, for three reasons. Firstly, there has been a large increase in their use since their genesis in the late 1980s (Vancheri et al., 2016, Feely et al., 2000, Charlesworth et al., 2015). Secondly, they are a commonly used drug (Walley et al., 2005, DeWilde et al., 2003); in Ireland, atorvastatin was the second most frequently prescribed medicine reimbursed by the State (Health Service Executive, 2016, p.159). Thirdly, much debate has ensued about the expansion of their use, particularly for primary prevention of cardiovascular disease (CVD) (Redberg and Katz, 2016, Steel et al., 2017, Demasi, 2018, Goldacre and Smeeth, 2014). For these reasons, I believe that the use of statins for primary prevention of CVD offers rich ground for analysing the process of medicalisation and to examine the difficult question as to whether it is possible to demarcate, in this context, the thin line between the appropriate use and the overuse of medicine. In this context it is important to note that any such demarcation will vary according to patient preferences; a further complication in attempts to judge what exactly constitutes appropriate use.

## **1.2 Statins**

This section describes the trajectory of statin development and use. In Section 1.2.1, I outline the mode of action of statins and describe the scientific breakthroughs that identified the link between cholesterol and CVD which led to the discovery and development of the drug. In Section 1.2.2, I describe the development of health policy in Ireland relating to CVD, while in Section 1.2.3 trends in statin use, in both the Irish and international contexts, are discussed.

### **1.2.1 The Development of Statins**

Statins, also known as HMG-CoA reductase inhibitors, are cholesterol-lowering drugs that act by inhibiting cholesterol biosynthesis in the body. Their mode of action is to mimic and displace the naturally occurring enzyme HMG-CoA reductase and, by fitting into the enzyme's active site in the body, compete with it. This interferes with the ability of HMG-CoA reductase to produce mevalonate, a molecule involved in the production of cholesterol. By this interaction, the conversion of HMG-CoA reductase to L-mevalonate is prevented and therefore the pathway for synthesising cholesterol in the liver is blocked. The liver cannot produce cholesterol and the level of circulating cholesterol in the bloodstream drops (Gazzerro et al., 2012).

In the early twentieth century, atherosclerosis or 'hardening of the arteries' was identified as a degenerative part of ageing and researchers began to search for the underlying mechanism that caused this (Greene, 2007, p.154). The structure and role of the molecule, now known as cholesterol, was described in 1932 (Bernal, 1932). In the late 1940s the Framingham study, a population-based study to determine the factors associated with the development of coronary heart disease (CHD), was undertaken and the statistical association between CHD and cholesterol was reported in 1957 (Greene, 2007, p.157).

The results of the first major trial to demonstrate the effectiveness of reducing cholesterol levels was published in 1984. 'The Lipid Research Clinics Coronary Primary Prevention Trial' (LRC-CPPT) demonstrated the effectiveness of a bile sequestrant, cholestyramine, a precursor of modern statins (Rifkind, 1984). The study included individuals whose only risk factor was high cholesterol and excluded those with diabetes, hypertension and prior

CVD. The primary end-point of the trial was ‘definite coronary heart disease death and/or definite nonfatal myocardial infarction’ and relative reductions of 24% in definite CHD death and of 19% in nonfatal myocardial infarction were reported in middle aged men with cholesterol levels over 265mg/L (6.8mmol/L). The cumulative seven-year incidence of the primary end point was 7.0% in the cholestyramine group, compared to 8.6% in the placebo group giving an absolute risk reduction of 1.6% and a relative risk reduction of 19.0%. The risk of death from all causes was only slightly, though not statistically significantly, reduced in the cholestyramine group. Greene (2007, p.170) notes that the drug was unpleasant to take and it was unlikely that this ‘odiferous gravel’ would gain traction among the public.

Nonetheless, despite such misgivings, Merck subsequently developed lovastatin, the first of the class of drugs now known as statins in the late 1980s. One month after the launch of lovastatin, the National Cholesterol Education Program launched the first US national guidelines for the detection and treatment of high blood cholesterol (Greene, 2007, p.178-190). In 1987 the European Atherosclerosis Society issued its first policy statement on strategies for prevention of CHD (European Atherosclerosis Society, 1987), for the first time recommending total cholesterol (TC) levels that warranted treatment with statins.

### **1.2.2 Irish Cardiovascular Health Policy**

In 1998 the Minister for Health and Children in Ireland established the Cardiovascular Health Strategy Group as part of an overall initiative on cardiovascular health and cardiac services. The group was to develop a strategic approach to reduce avoidable death and illness caused by cardiovascular disease and in 1999 published the *Building Healthier Hearts – Report of the Cardiovascular Health Strategy Team* (Department of Health & Children, 1999). In the context of primary prevention of CVD, the report emphasised lifestyle modification and that professionals in the primary care services should provide ‘personalised advice on healthy lifestyles to clients’. At the time, the Group did not recommend risk assessment check-ups or screening for whole groups of the population, but rather a combination of ‘opportunistic and systematic risk assessment, with a very structured approach to the management of those identified as being at high risk’. (Department of Health & Children, 1999, p.70).

A series of Irish academic papers followed the publication of this report that reinforced the recommendation of managing those at high risk of CVD. For example, Feely (1999) emphasised the need for hospitals and cardiologists to ‘take ownership’ of new guidelines on CVD and particularly promote cholesterol-lowering in secondary prevention. In 2000, the same author reported that while the use of statins was rising rapidly, utilisation was below targets and was not directed at the population most likely to benefit (Feely et al., 2000). The same year a newsletter for GPs was issued (Anon, 1999) that reported that in Ireland, one fifth of adults were at risk of CHD because of high cholesterol levels and that this presented a major economic burden to the Irish health service. While the newsletter recommended lifestyle and dietary modification as key components of the management of hyperlipidaemia, these, according to the authors, might ‘not achieve treatment goals’. In 2005, an analysis of statin prescribing trends was published that reported an increase in statin use (Teeling et al., 2005). However, the authors asserted that data on the optimal use of statins ‘may not have been fully understood by prescribers in primary care, resulting in the under-prescribing of statins’ (Teeling et al., 2005).

In 2010 a new National Cardiovascular Health Policy (2010 – 2019) was published (Department of Health & Children, 2010), which noted:

Cardiovascular disease remains the most common cause of death in Ireland, currently accounting for one-third of all deaths and one in five premature deaths. However, there has been substantial progress. Age-standardised death rates from cardiovascular disease have decreased by two-thirds over the past 30 years. Despite improvements, Ireland still ranks below the EU15 average for life expectancy for both men and women ... In primary care, prescriptions for cardiovascular medication have increased two- to four-fold ... A much greater level of analysis of the costs of cardiovascular disease is needed to inform discussions about service investments and value for investment over the 10-year timeframe of this new policy (Department of Health & Children, 2010, p.2).

The policy recommended that the 2007 European Society of Cardiologists Clinical Practice Guidelines (Graham et al., 2007) should be adopted and that a care protocol for primary care based on these guidelines should be developed. The report outlined that

CVD, at this point, was the single largest cause of death in Ireland, accounting in 2008 for 35% of all deaths, and that:

Effective prevention requires a shift of the entire distribution of a risk factor (e.g. raised cholesterol) to lower values. It should extend beyond a focus on high-risk individuals, utilising cholesterol-lowering therapies, to population-based approaches, preventing the development of the risk factors themselves (Department of Health & Children, 2010, p.65).

In summary, the differences in recommendations of the 1998 and 2010 cardiovascular health policy documents suggest a shift in emphasis from targeting high-risk individuals to a population-based approach, whereby prevention of CVD became the focus of intervention. The increasing focus of medicine on preventative health and surveillance of ‘at-risk’ people is a feature of medicalisation (and is discussed in greater detail in the next chapter), and may in part have motivated the increase in statin use, which is now described.

### **1.2.3 Trends in Statin Utilisation**

As noted at the start of this chapter, statins were chosen as the focus of this thesis because they are an exemplar of the medicalisation process. Statins were first licensed in 1987 and the dramatic increase in their use over time illustrates one key feature of the process of medicalisation, the expansion in the use of a medicine. In this sub-section I will outline some of the research examining trends in statin use in Ireland, Europe and in other countries, using a range of data types and sources. Trends in statin use tend to be reported either as proportions of populations who are using statins or as daily defined doses. Thus, in some circumstance, it is not feasible to fully compare data without additional information. Despite this, it is possible to demonstrate that according to data from several countries, including Ireland, that there has been a large increase in statin use since the early 1990s.

### *Trends in Ireland*

Much of the following analysis of statin use in Ireland is based on data from the General Medical Services (GMS) scheme, which is part of Ireland's Primary Care Reimbursement Service (PCRS), details of which are described in Box 1.1.

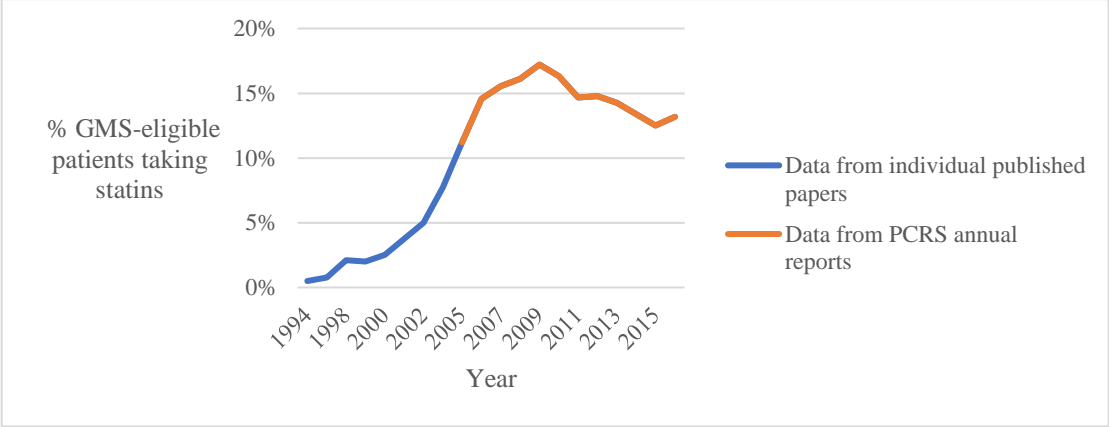
#### Box 1.1: Primary Care Reimbursement Service Data

The health system in Ireland is two-tiered comprising both publicly and privately funded elements. The Health Service Executive's (HSE) PCRS supports the delivery of a wide range of primary care services to the general public. The largest of the PCRS schemes is the GMS scheme under which approved drugs, medicines and appliances are provided through community pharmacists and processed and paid for by the PCRS. However, eligibility for this scheme has changed over the period since the introduction of statins in 1987 and thus the following analysis may include slight variations to the population covered by the scheme, which is discussed in more detail later. Nonetheless, for the purposes of this narrative description of the increase in statin use over time, PCRS-GMS data are adequately informative.

The earliest analysis of the prevalence of statin use in Ireland was conducted by Feely et al. (2000) who reported a four-fold increase in the use of lipid-lowering drugs, 92% of which were statins, between 1994 and 1998. Overall, approximately 0.50% of the GMS eligible population were taking statins in 1994 (0.52% of GMS-eligible women and 0.47% of men). This rose to just over 2% by 1998 by which time more men were taking statins than women. Teeling et al. (2005) conducted a similar study between 1998 and the end of 2002, reporting a rise from about 2.0% to 7.7% of GMS patients who were taking statins. Walley et al. (2005) reported a 274% increase in statin use in Ireland between 2000 and 2003, an average increase of approximately 54% per year. From 2005, the annual reports on the PCRS disaggregated statin expenditure and frequency of use from other cardiovascular drugs. Based on this data, the proportion of GMS eligible people taking statins rose from approximately 11% in 2005 to over 17% in 2009 and

gradually fell over subsequent years to 13% in 2016. These various estimates are collated and presented in Figure 1.1.

Figure 1.1: Proportion of General Medical Service Eligible Patients Taking Statins



Sources: Feely (1999), Teeling (2004) and PCRS annual reports.

Note: Estimates up to and including 2003 are based on Figure 2 in Teeling (2004), there are no data available for 2004, and estimates from 2005 onwards are based on data from PCRS reports. These latter estimates were calculated using data on the types, dosages and frequency of statins reimbursed through the GMS in June 2016 in Ireland, with the number of people taking statins estimated from the number of items reimbursed, as reported in each of the annual PCRS reports from 2005 onwards. PCRS reports before 2005 do not disaggregate statins from other cardiovascular drugs.

*International Trends*

While the previous discussion focuses on the Irish context, it is also important to consider the utilisation of statins internationally. Increases in statin utilisation have been reported globally (O’ Keeffe et al., 2016, Wallach Kildemoes et al., 2008, Selmer et al., 2009, Rikala et al., 2013, Gu et al., 2015, Ma et al., 2013, Minard et al., 2016, Raymond et al., 2007). For example, in an analysis of twelve European countries, Vancheri et al. (2016) found that on average statin utilisation increased by more than 400% between 2000 and 2012. Among those aged 65–79 years in the US, Charlesworth et al. (2015) found that between 1988 and 2010, there was an increase in the proportion of adults on one or more statin from 2% to 42.5%. Also in the US, Gu et al. (2015) reported that statin use increased from 16% to 23% in adults aged 40 and over from 2003 to 2012. Minard et al. (2016) reported an increase from just over 5% to 21% in the percentage of Nova Scotia Seniors' Pharmacare program beneficiaries aged 65 years and older who were dispensed statins between 1999 and 2013.

### *Comparison of Irish and International Trends in Statin Utilisation*

Walley et al. (2004) reported an average increase of 36% in statin use in ten European countries in the five years between 1997 and 2002. The lowest increase reported was in France (56%) and the highest in Ireland (274%). The reasons for this are not clear, although Walley et al. (2005) note that the patients included in the databases used for the analysis may have comprised older and sicker patients in the Irish data compared to other countries. Furthermore, Ireland recorded a relatively low use of statins at baseline compared to some other countries. However, Ireland's increase far exceeded other comparable countries that started from a low base. Another factor that may have influenced the trend is that there was little use in Ireland of fibrates, considered at the time to be a pharmaceutical alternative to statins, compared to France, the country that recorded the lowest increase in statin use.

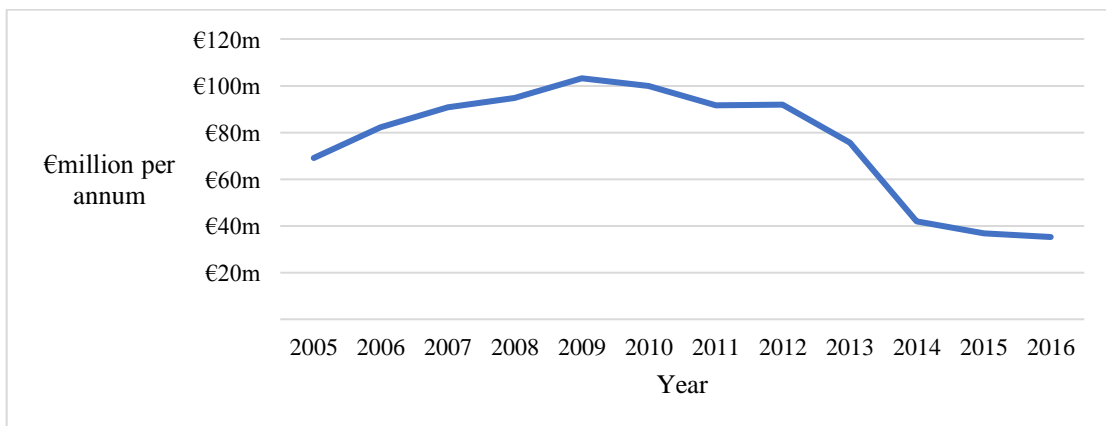
The decrease in statin use in Ireland from 2009 onwards (Figure 1.1) may be attributable to several factors. For example, the makeup of those eligible for reimbursement by the GMS scheme has changed over the period. In 2008, 17% of medical card holders were over 75 years and by 2016 this fell to 13% (Connors, 2017b, p.9). Over-75s are higher prevalent users of statins than other age-groups and so a fall in the proportion of over-75s could contribute to the decline reported. Furthermore, trends in the use of other cholesterol lowering drugs such as cholesterol absorption inhibitors, ion exchange resins, fibrates and PCSK9 Inhibitors may have impacted statin use, though analysis of those trends is beyond the scope of this thesis. Walley et al. (2005) noted the impact of 'aggressive marketing' on statin use between 1997 and 2003 and as statins have come off patent, there may have been less marketing by the pharmaceutical industry of statins to doctors. (This is an issue that is considered in the analysis in Chapter 7). However, decreases in statin use have not been reported in recent analyses from other countries (Minard et al., 2016, Hsieh et al., 2017, O' Keeffe et al., 2016, Salami et al., 2017). Furthermore, in relation to the decline in statin use in Ireland, it is important to note that PCRS data describe only aggregate data from publicly funded patients and it is not possible to report the use of statins by gender or age, whether the statin is prescribed for primary or secondary prevention, or by those who are not reimbursed by PCRS.

In summary, there has been a large increase in statin use from the late 1990s in Ireland and in other countries. In Ireland this increase seems to have plateaued or fallen since 2009, while the data examined from other countries do not exhibit a decrease.

### *The Cost of Statins*

The use of statins exerts considerable pressure on health care resources both internationally and in Ireland. Worldwide, despite the expiration of their patents, total sales of statins are expected to reach US\$1 trillion by 2020 (Demasi, 2018). In Ireland, the cost of statins reimbursed by the PCRS increased from €65m in 2005 to a peak of over €100m in 2009, falling to €35m in the GMS scheme in 2016 (see Figure 1.2). Disaggregated cost data are not available from PCRS before 2005, when annual reports only report figures for cardiovascular drugs in general.

Figure 1.2: Cost of GMS Reimbursed Statins in Ireland



The large reduction in the cost of statins to the Irish State (Figure 1.2) compared to the relatively smaller and recent reduction reported in their use (Figure 1.1) may be explained by several factors. First, many statins have come off-patent during that period resulting in a fall in costs (La Mattina, 2016). Secondly, in an agreement between the Irish government and the pharmaceutical industry, savings of €250m were reported in total drug expenditure by the State between 2006 and 2010. This was achieved by linking the price of new medicines in Ireland to nine EU member states (Walshe and Kenneally, 2013). Previous to this, the price of medicines in Ireland were linked to the currency adjusted wholesale price in the UK, or the average of the wholesale price in Denmark, France, Germany, the Netherlands and the UK (whichever was lower), which were ‘high

priced' EU member states (Barry, 2008). Following the agreement with the industry, the prices of medicines in Ireland were linked to countries whose average price was lower. In addition, reference pricing for the individual patient was established. Reference pricing means that a price for an original branded medicine and its generic is set by the HSE, and this was the price that the HSE would reimburse to pharmacies, regardless of the individual medicines' prices (Department of Health & Children, 2014). If the patient wishes to obtain the original product, they have to pay the difference between the reference price and the branded product's price. Atorvastatin, the most commonly prescribed statin in the PCRS, was the first drug to be reference priced in 2013, achieving a reduction of 70% in the price the HSE had previously paid to reimburse the product (Department of Health & Children, 2014). In addition, the GMS pharmacy dispensing fee system was restructured in 2009 realising savings for the PCRS (Walshe and Kenneally, 2013). Another cost-containment initiative introduced in 2013 was the preferred drug initiative, the purpose of which was to encourage prescribers to use a certain, cheaper version of a commonly prescribed drug (Health Service Executive, 2018). For statins, the preferred drug was deemed to be simvastatin, the cheapest of the statins used in Ireland.

### **1.3 Debates on Statins**

As previously noted, medicalisation can lead to overuse of medicine, and the expansion of the use of interventions that provide little benefit for many recipients has been especially criticised. The use of statins in both primary and secondary prevention of CVD has provoked debate from the very beginning of statin use but has been largely focused on the central criticism of medicalisation; does the increase in use of statins, particularly in low-risk people, represent a positive or negative development? For this reason, in this section, I focus on some of the debates that might inform that judgement.

The earliest trial to demonstrate the benefits of lowering cholesterol was the LRC-CPPT, the results of which were reported in January 1984 by the National Heart, Blood and Lung Institute (NHLBI) in the US. The authors reported that those taking a bile-acid sequestrant, cholestyramine, had lower rates of death from CHD and non-fatal heart attacks. The results were widely publicised and the NHLBI set up the Consensus Conference on Lowering Cholesterol to Prevent Heart Disease, which then enacted the

National Cholesterol Education Program (NCEP). Greene (2007, p.170) reports that while the results of the study were described at the time as ‘definitive proof’ of the benefits of lowering cholesterol, controversy arose almost immediately. The original publication of the study acknowledged that the results ‘could be narrowly interpreted to apply only to the use of bile-acid sequestrants in middle aged men with cholesterol levels above 265 mg/dL’ (6.8mmol/L). Despite this, the next sentence noted that ‘the trials implications, however, could and should be extended to other age groups and women and, since cholesterol levels and CHD risk are continuous variables, to others with more modest elevations of cholesterol levels’ (Greene, 2007, p.171).

Although the consensus conference was, as the name suggested, designed to create consensus, many doctors, statisticians and policy makers cited the LRC-CPPT as an example of a ‘poor study with low generalizability, dubious post-hoc statistical wrangling, clinically insignificant demonstration of the preventative power, and wildly unsupported extrapolation in generalizing the results of the study’ (Greene, 2007, p.171). One of the most prominent critics at the time was cardiovascular researcher and doctor Michael Oliver, who noted that the aim of the conference was to ‘try to create a consensus view ... that all levels of blood cholesterol in the United States are too high and should be lowered’ (Oliver, 1985). In 1987, a model was published in the *Annals of Internal Medicine* (Taylor et al., 1987) that demonstrated that even if the LRC-CPPT results were valid, the recommendation would only result in adding eighteen days to the average American’s life ‘at a significant cost to comfort and pocketbook’ (Greene, 2007, p. 177). Also in 1987, the first statin, Mevacor (lovastatin) was launched amid controversy concerning the impartiality of the NCEP expert advisors (Moore, 1989), a controversy which has continued to more recent times (Roberts, 2006).

The debate for and against statin use continued from the 1980s onwards in medical journals (Redberg and Katz, 2012b, Redberg and Katz, 2012a, Perlmutter et al., 2013, Abramson et al., 2013, Strandberg, 2014, Goldacre and Smeeth, 2014, Goldacre, 2014, Schwitzer, 2016, Demasi, 2018, Steel et al., 2017, Armitage, 2007, Vaughan et al., 1996, Ray et al., 2014, Talbert, 2006, Blumenthal, 2000) and several books have been written on the subject of statins specifically or including statins as an example of overuse or medicalisation (Moynihan et al., 2002, Welch et al., 2011, Dumit, 2012, Cassels, 2012,

Roberts, 2012). However, the more recent controversy about statins, particularly in the context of primary prevention, is best exemplified by the debate that arose in 2014 between *The British Medical Journal* (*The BMJ*) and the Cholesterol Treatment Trialists Collaboration (CTT).

In 2010 a CTT study was published in *The Lancet*. This consisted of a meta-analysis of 27 previously published randomised controlled trials (RCTs) on the effects of lowering LDL cholesterol with statin therapy on people at low risk of vascular disease (Mihaylova et al., 2012). The study found that for people whose 5-year risk of major vascular events was lower than 10%, the benefit of statin treatment ‘greatly exceeds any known hazards of statin therapy’. According to clinical guidelines at the time, these low-risk people would not be typically regarded as suitable for LDL-lowering statin therapy. However, the CTT authors concluded that ‘these guidelines might need to be reconsidered’. This evidence was used by the Cochrane Collaboration in their updated review of the use of statins for primary prevention in 2013 (Taylor et al., 2013), reversing the conclusions from their earlier analysis published just two years previously (Taylor et al., 2011). The new review stated that the evidence now justified the use of statins in people at low risk of cardiovascular disease. Prof. Rory Collins of the CTT had been highly critical of the Cochrane 2011 analysis for not including evidence from the CTT’s previous paper published in 2010 (de Lemos et al., 2010) and his correspondence with Cochrane is included as an appendix to the 2013 review (Taylor et al., 2013).

In October 2013, *The BMJ* published two related articles. The first, ‘Should people at low risk of cardiovascular disease take a statin?’ by John Abramson, from the Harvard Medical School, stated that statin therapy in low-risk people did not reduce all-cause mortality or serious illness, and had an 18% risk of causing side effects (Abramson et al., 2013). The second, ‘Saturated fat is not the major issue’ by Aseem Malhotra, a British cardiologist working in the National Health Service, stated that high total cholesterol is not a risk factor in a healthy population and that 20% of patients who took statins in a recent study (Zhang et al., 2013) discontinued because of unacceptable side effects (Malhotra, 2013). However, the study by Zhang et al. (2013), on which both authors had based their conclusions regarding the safety of statins, had in fact established associations

between statins and adverse events in 17.4% patients in the study, but had not established causality.

Rapid responses to *The BMJ* articles ensued, including from one of the authors of the Cochrane report, Mark Huffman, and both Abramson and Malhotra. However, the Guardian newspaper had already published an article on the controversy by Sarah Boseley, which considerably raised the temperature. In this piece entitled ‘Doctors’ fears over statins may cost lives, says top medical researcher’ (see Figure 1.3), Collins asserted that the uncertainty created by the articles could lead to the loss of life. Collins also stated that statins were very well tolerated and that claims about significant side effects were misleading (Boseley, 2014).

Figure 1.3: Boseley’s Article in *The Guardian*

## Doctors' fears over statins may cost lives, says top medical researcher

**Prof Rory Collins accuses GPs of unjustifiable suspicion of cholesterol-reducing drugs, but is himself accused of 'fear-mongering'**

● **Statins for all: do the benefits outweigh the risks?**



In May 2014, Fiona Godlee, the editor of *The BMJ*, published an editorial explaining what had happened, how the articles came to be published, and how Collins had been offered rapid responses or an article in *The BMJ*, but that he had declined these offers (Godlee, 2014a). Godlee also announced she was setting up an independent review board to decide whether the articles should be retracted. Several articles and responses in *The BMJ* ensued, including Ben Goldacre and Liam Smeeth's editorial 'Mass treatment with statins' (Goldacre and Smeeth, 2014). Goldacre and Smeeth pointed out that mass treatment of a healthy population for a possible future risk is a very different type of medicine from therapeutics, whereby a doctor treats a sick patient. This type of medicine presented new challenges and required 'wholesale structural improvements in how we gather and communicate research evidence' and pointed to a lack of reliable information from randomised trials on common side effects of statins. In August 2014, Godlee published an editorial outlining the conclusions of the independent panel, (Godlee, 2014b) which stated that the articles should not be retracted (Heath et al., 2014). The panel also called for anonymised individual patient data (IPD) from the clinical trials of statins to be made available for independent scrutiny. Godlee emphasised the significance of this point, and outlined how at that time, only the drug companies, the trialists, and the CTT collaboration in Oxford had access to IPD from the statin trials. The Cochrane review group did not have access to this information either, and so based its revision on the CTT conclusions, as well as other published data.

*The BMJ* subsequently wrote to the Cochrane review group and the principle investigators (PIs) of the CTT studies asking them to release this data. Cochrane were noncommittal in their reply but seven PIs from the original CTT trials responded saying they were potentially willing to share the data with other researchers. Collins and his CTT colleagues replied to *The BMJ* confirming that their meta-analyses were limited to patient level data on cause-specific mortality, major vascular events, and site-specific cancers. They had not analysed data on other adverse events, as these were not part of the original CTT agreement. The Express newspaper took up the story, in which Collins was quoted as saying his team would carry out a challenging reassessment of side effects (Johnston, 2015) (Figure 1.4). Godlee, in the article stated: 'This is of real concern. We wrongly assumed all the details of possible side effects had been thoroughly assessed before new guidance effectively made tens of thousands of people eligible for this drug.'

Figure 1.4: Johnston's Article in *The Express*



In February 2015, Nigel Hawkes, writing in *The BMJ*, announced that the CTT planned to produce tabulated results of all side effects of statins recorded in the trials, by the end of the year (Hawkes, 2015). *The BMJ* also reported that England's Chief Medical Officer had asked for a review of drug evaluation in the wake of the statin controversy (Wise, 2015). In September 2016, a review of the evidence for the safety and efficacy of statin therapy was published in *The Lancet* (Collins et al., 2016). The lead author was Rory Collins of the CTT but the paper was co-authored by a wide range of academics and medical professionals. The aim of the review was to provide 'the appropriate interpretation of evidence' and 'how evidence from randomised trials yields reliable information about both the efficacy and safety of statin therapy'. The paper criticised 'how claims that statins commonly cause adverse effects reflects a failure to recognise the limitations of other sources of evidence'. Their findings strongly supported the use of statins in both primary and secondary prevention of CVD and expressed concern that

reports of adverse effects may be responsible for the underuse of statins among individuals at increased risk of CVD.

Krumholz (2016) subsequently commented in *The BMJ* on the limitations of this review. He pointed out that trial populations do not generally reflect the diversity of patients seen in practice. For example, few of the statin trials included people over the age of 80. He wrote that many of the trials were underpowered to detect relevant harms and that the comparability of harm data was not clear. In addition, he stated that the comparative effectiveness and safety of individual statins is unexamined. While Collins' review criticised the use of observational data to analyse adverse reactions to statins, Krumholz argued that the only readily available evidence is observational and it is unlikely that trials would be conducted in the future to address these questions about statins. For consensus to emerge, Krumholz suggests it would have been more useful if data from the statin trials were made public so that others could independently analyse them.

An editorial in *The BMJ* was published on 15<sup>th</sup> September (Godlee, 2016) that reiterated that '(i)ndependent third party scrutiny of the statins trial data remains an essential next step'. Godlee reported that she had written to England's Chief Medical Officer to ask for her to call for and fund an independent review of the evidence on statins. In 2017, in an article published in *The Lancet*, Godlee (2017) noted that:

Questions about the evidence base for statins continue to emerge from many quarters: how strong is the evidence, how large is the benefit for individuals at lowest risk of heart disease, how well did the trials record common minor side-effects, how representative were the trials of women and the elderly ... why is there a discrepancy between the real-life experience of muscle pain and what was reported in the trials, why have the data for harms not yet been given the same levels of scrutiny as the data for benefits, and is cholesterol a reliable surrogate endpoint to guide prevention of cardiovascular disease?

She justified and reiterated calls for independent review of the raw data because statins 'are already the most widely prescribed class of drug in high-income and middle-income countries'. However, up to June 2016, only eight researchers, from a total of 183 trials

had responded to *The BMJ*'s calls for access to the raw data from statin trials with the aim of characterising adverse outcomes from both published and unpublished information. All eight said they were potentially willing to share their data with other researchers but to date no further data has been accessed.

## **1.4 Research Aims and Objectives**

The overall aim of this thesis is to explore the medicalisation of primary prevention of cardiovascular disease through the use of statins from the perspective of society as a whole, as well as from that of the individual, and to examine if it is possible to demarcate the thin line between the appropriate use and the overuse of medicine. This overall aim is informed, in part, by the ongoing debate about statins, as described above, which highlighted some of the impacts of the expansion in the use of statins that need to be considered, particularly in primary prevention. These include, for example, whether the medicalisation of healthy people is appropriate, whether the evidence to support statin use in primary prevention is robust, and whether the financial burden statin use imposes on overstretched health care systems can be justified. These are all considerations that could assist in delineating the line between appropriate use of this medicine and overuse and waste. As a result, whether or not medicalisation in this context represents a 'positive development' needs to be examined in a number of ways, since 'there are many different ways of interpreting the world and undertaking research, [such] that no single point of view can ever give the entire picture' (Saunders, 2012 cited in Dudovskiy, 2018).

In order to address the overall aim, this thesis addresses six specific, yet interconnected, research objectives/questions in six separate chapters. These are as follows:

1. What is medicalisation, how does it happen and how does medicalisation relate to the use of statins for primary prevention of CVD? (Chapter 2)
2. What is the prevalence of statin utilisation amongst older people in Ireland and what factors are associated with the likelihood of using a statin, particularly in primary prevention of CVD? (Chapter 3)
3. What is the evidence, from exclusively primary prevention data, on the effectiveness of statins for the prevention of CVD and stroke? (Chapter 4)
4. What are the potential impacts of changes to clinical guidelines for the prevention of CVD on eligibility for statin therapy, cost and number-needed-to-treat to

prevent one major vascular event and how do these relate to patient preferences?  
(Chapter 5)

5. How is preventative health, risk and ‘candidacy’ for statin treatment perceived and negotiated by patients and doctors according to existing literature in the context of statins for primary prevention of CVD? (Chapter 6)
6. How do patients, physicians and others in Ireland define and construct the cardiovascular ‘disease regime’ and how does this relate to the concepts of medicalisation and governmentality? (Chapter 7)

Thus, overall, this thesis presents six discrete pieces of research, but follows a logical chain of evidence (O' Cathain, 2009) so that the overall aim can be realised. Firstly, in Chapter 2, by situating the primary prevention of CVD within the literature on medicalisation, the genesis and trajectory of statin use can be compared to the theoretical processes of medicalisation, thus establishing whether primary prevention of CVD has indeed been medicalised. Secondly, by examining the prevalence of use and the evidence to support that use in Chapters 3 and 4, the current use of statins and current evidence can be explored and quantified. Thirdly, by assessing the impacts of changing clinical guidelines in Chapter 5, some of the effects of a medicalisation process can be illustrated. Finally, I argue that because societal attitudes and values enable medicalisation, the perceptions and reported behaviours of doctors, patients and others who may influence statin use should be considered, and this is done in Chapters 6 and 7.

## **1.5 Methodology and Data**

The chapters described above represent discrete pieces of analysis whereby quantitative and qualitative data, as well as the findings of an overview of systematic reviews, were collected and analysed. In this section I outline the methodological stance and research design underpinning this approach and thesis.

To begin, it is useful to distinguish between ‘methodology’, ‘research design’ and ‘methods’, and Creswell and Plano Clark (2017) provide a helpful summary. They state:

*A methodology refers to the philosophical framework and the fundamental assumptions of the research. Because the philosophical framework one uses*

influences the procedures of research, we define methodology as the framework that relates to the entire process of research. Research *design* refers to the plan of action that links the philosophical assumptions to the specific methods. Experimental research, survey research, ethnography and mixed methods are all research designs. *Methods*, on the other hand, are more specific. They are techniques of data collection and analysis, such as quantitative standardized instrument or qualitative theme analysis of text data. (Creswell and Plano Clark, 2017, p.4)

Because of the very different philosophical frameworks that inform different sections of this thesis, the methodologies are eclectic. Kroos (2012) describes eclecticism as ‘an inevitable outcome of any scientific enterprise within which different theoretical positions allow us to grasp the meaning of interrelationships between different objects and their properties’. The aim of mixed methods is to combine qualitative and quantitative research traditions, which can be, but are not necessarily associated with different philosophical standpoints, and eclecticism represents a ‘middle way’ of combining the two (Schneider, 1998 cited in Kroos, 2012). Thus, the philosophical stance of eclecticism serves ‘as the ideal for intellectual freedom’ (Schneider, 1998), and allows the research approach of this thesis to be considered as quantitative *as well as* qualitative (Schneider, 1998 cited in Kroos, 2012).

The research design of the thesis is that of mixed methods, which ‘involves collecting, analyzing, and interpreting quantitative and qualitative data in a single study or in a series of studies that investigate the same underlying phenomenon’ (Leech and Onwuegbuzie, 2009). Creswell et al. (2011) argues that problems most suitable for mixed methods are ‘those in which the quantitative approach or the qualitative approach, by itself, is inadequate to develop multiple perspectives and a complete understanding’. Quantitative research methods focus on questions that demand numerical answers and are traditionally associated with the natural sciences, the branch of science dealing with the physical world, and objectively measurable phenomena. Quantitative research, thus, is considered ‘positivist’, based on the assumption that reality is ‘a fixed, measurable reality external to people’ (Tuli, 2010). In contrast, qualitative research methods focus on questions that require a textual answer, are associated with the social sciences, and are primarily

concerned with ‘understanding human beings’ experiences in a humanistic, interpretive approach’ (Jackson et al., 2007). Thus, combining the two, a mixed methods approach:

... provides more comprehensive evidence for studying a research problem than either quantitative or qualitative research alone. Researchers are given permission to use all the tools of data collection available rather than being restricted to the types of data collection typically associated with qualitative or quantitative research. (Creswell and Plano Clark, 2017, p.9).

As described above, the aim of this thesis is to explore the medicalisation of primary prevention of CVD through the use of statins from the perspective of society as a whole, as well as from that of the individual, and to examine if it is possible to demarcate the thin line between the appropriate use and the overuse of medicine. While the use of statins and evidence to support their use can be quantified, factors which influence that use are not overtly visible without examining the issue from a qualitative perspective. Nor can the delineation of appropriate use and overuse be fully considered without the input of those prescribing and using statins. The personal and professional experiences of statin users and prescribers offers an opportunity to enrich this research process and provides an opportunity for exploring the ‘big picture’ perspective of statin use. Thus, the use of mixed methods was considered to be the best approach to achieving the research aim.

Creswell et al. (2011) describes a number of types of mixed methods designs, and based on this classification, this thesis can be considered a ‘multiphase sequential mixed methods design’. It is ‘multiphase’ because it consists of ‘multiple studies, some quantitative and some qualitative, that build on each other and contribute to an overall program objective or purpose’ (Creswell et al., 2011). It is sequential because ‘one dataset builds on the results from the other’. For example, while Chapters 3 to 7 are ‘stand-alone’ discrete pieces of work that have submitted for publication in peer-reviewed journals as single pieces of analysis, they each contribute to the common overall objective, that is, a more complete understanding of medicalisation in the context of primary prevention of CVD. In addition, there is a natural iterative aspect to the development of the chapters, the findings of one causing the reconsideration and refocussing of others, as I describe in more detail in Chapter 8.

Finally, the specific methods employed within the individual studies in this thesis, that is, the techniques of data collection and analysis, are described in detail in the individual chapters.

## **1.6 Overview of Thesis**

Following this introduction chapter, the next six chapters address the specific research objectives/questions of the thesis. To begin, Chapter 2 comprises a broad scoping literature review of the topic of medicalisation. Here I outline the literature on medicalisation in general; what it means; what it is driven by, and by whom; and how medicalisation relates to the use of statins for primary prevention of CVD. In this way, I justify why the use of statins in primary prevention of cardiovascular disease is an exemplar par excellence of medicalisation.

The subsequent five chapters comprise the main analysis from my PhD research and are presented in the format in which they have been either published in, or submitted to, peer-reviewed academic journals (the publication status of each chapter/article is described in Section 8.4.1.). Thus, it is important to note that the general style, structure and layout differs across these chapters, as a result of the different guidelines associated with the different journals. Some of these differences are also reflective of the mixed methodology employed throughout the thesis, as described above.

Building on the literature review in Chapter 2, the starting point of analysis is to ascertain who are using statins in Ireland today and for what purpose. In particular, Chapter 3 describes the prevalence of statin utilisation by people aged over 50 years in Ireland and the factors associated with the likelihood of using a statin, focusing particularly on those using statins for the primary prevention of CVD. This is a cross-sectional analysis of cardiovascular risk and sociodemographic factors associated with statin utilisation from Wave 1 of The Irish Longitudinal Study on Ageing (TILDA).

Once the prevalence of statin use in primary prevention is established in Chapter 3, the next objective is to evaluate the evidence to support that use. To that end, Chapter 4 comprises an overview of systematic reviews of data from *exclusively* primary prevention of cardiovascular disease. The rationale for conducting the overview was that while many

statin users fell into the primary prevention category, most systematic reviews include a proportion of participants from the secondary prevention category.

The use of medicine is influenced, among other things, by the clinical guidelines that inform doctors and policymakers of the most up-to-date recommendations in a particular clinical area by experts in that field. Clinical guidelines change over time and have generally widened the numbers of people who are potentially eligible for a medical intervention (Moynihan et al., 2013). In Chapter 5 I explore the impacts of changing cardiovascular clinical guidelines. A cohort of people aged over 50 without established CVD from TILDA are analysed to determine their eligibility for statin therapy based on seven consecutive European clinical guidelines. The associated potential cost is modelled, as well as the numbers-needed-to-treat to prevent one major vascular event in patients at the lowest baseline risk for which each guideline recommends treatment. These are compared to the published numbers-needed-to-treat that patients report is required to justify taking a daily medicine.

Chapters 6 and 7 are closely related and comprise the qualitative section of the thesis. Chapter 6 is a broad scoping review of the literature on how preventative health, risk and ‘candidacy’ for statin treatment are perceived and negotiated by clinicians and patients in this context. How the evidence and knowledge about cardiovascular risk reduction are constructed, interpreted and communicated are examined, as is how a patient’s gender, socio-demographic and cultural differences impacts patterns of statin use. Chapter 7 is informed by the concepts of governmentality and medicalisation and aims to examine the ‘type of assumptions, of familiar notions, of established, unexamined ways of thinking the accepted practices’ (Foucault, 1994 [1981]) on which the Irish cardiovascular disease regime is based. Semi-structured interviews were conducted with those ‘at risk’ of cardiovascular disease, their doctors and other professionals whose opinions were felt to be pertinent or influential within this discourse and a post-structural policy analysis approach was used to analyse the transcripts. Full details of the data and methods used are presented in the respective chapters.

Finally, Chapter 8 concludes this thesis and provides an overview and interpretation of the main research findings, while a ‘Research Impact Framework’ is used to describe the

potential impacts of these findings (Kuruville et al., 2006). These can be considered under four broad headings: research-related impacts; policy impacts; service impacts; and, societal impacts. In addition, the strengths and limitations of the research methodology and approach are also outlined in Chapter 8.

## 2 Medicalisation

*‘Medical science has made such tremendous progress that  
there is hardly a healthy human left’*

Aldous Huxley

### 2.1 Introduction

In this chapter I trace the genesis and trajectory of the concept of ‘medicalisation’ and review the work of key authors and themes. The medicalisation literature emerged in the 1960s and 1970s with writers such as Thomas Szasz and Ivan Illich, but the concept has shown sustained currency and debate surrounding medicalisation continues today. The considerable attention given to the topic by influential medical journals such as *The Lancet* and *The BMJ*, as well as journals within the social sciences, testifies to the enduring significance of the concept.

This chapter is structured as follows: Section 2.2 begins by outlining the literature search strategy that was employed for this chapter. Section 2.3 then defines medicalisation in its broadest sense and discusses other related and sometimes overlapping concepts. It describes the work of the earliest writers on medicalisation and considers how they theorise the process of medicalisation, including a brief discussion of the main actors in this process. Here I discuss how medicalisation relates to governmentality as theorised by the French philosopher Michel Foucault; that is, how a ‘regime of truth’ is established that allows the acceptance of the legitimacy of medical claims. In addition, I outline two main critiques of medicalisation. The first critique concerns the pejorative use of the term medicalisation; while the term is value-neutral according to some writers, others use it pejoratively. Secondly, the reductionist tendency of medicalisation to define problems as ‘medical’ risks, thereby ignoring the broader socio-economic determinants of health, is considered.

In Section 2.4, I draw out the relevance of the concept of medicalisation to the history of the prescribing of statins for cardiovascular disease (CVD) prevention and have particularly focused on the conceptual tools that are offered in this literature. Drawing heavily on the work of Jeremy A. Greene’s book *Prescribing by Numbers*, I use a

medicalisation lens to trace the trajectory of firstly, the identification of high cholesterol as a medical problem, secondly, the discovery of statins, and finally the recommendations for expansion of their use in clinical practice guidelines. There is no doubt that there has been medicalisation in the area of primary prevention of CVD, but whether this has been a positive or negative development is less clear. Building on the previous sections, in Section 2.5 I examine the overlap between medicalisation, over-diagnosis and overuse, the consideration of which, ultimately, is a central concern of this thesis. Finally, Section 2.6 concludes this chapter.

## **2.2 Literature Search Strategy**

I undertook a broad scoping review of the literature by first identifying relevant MeSH and Emtree terms, combinations of which were used in the relevant databases. Search terms, which were used singly and in combination, included *medicalisation; medicalization; overuse; disease mongering; indication creep; expanding disease definitions; pharmaceuticalisation; pharmaceuticalization; statins; hydroxymethylglutaryl-CoA reductase inhibitors; lipidaemia; lipidemia; cholesterol; hypercholesterolaemia; hypercholesterolemia; hypercholesterolemic agent; primary prevention; cardiovascular medicine; health economics; economics; media; medical economics*. I searched PubMed, Scopus, MedLine, EBSCO, EconLit, Business Source Complete for articles up to and including November 2015. Articles and abstracts were screened for relevance, using inclusion and exclusion criteria. I identified key articles and books and tracked the forward and backward citations of these. Articles were included if they comprised English language, peer-reviewed journal articles. I identified additional articles by using the reference and citation lists of the journal articles identified by the database searches. I undertook periodic reviews of the literature while writing the thesis and some further articles were identified during the review process.

## **2.3 Medicalisation and Related Concepts**

As outlined in the Chapter 1, medicalisation is conceptualised as a process whereby non-medical problems become defined and treated as medical problems (Conrad, 2005). The term itself does not imply a value judgement as to whether this change is good or bad, but merely notes that ‘the problems have moved into medical jurisdiction’ (Conrad et al.,

2010, p.1946). More recently, because of scientific developments, new terms have been introduced that relate to medicalisation or define it more specifically in different contexts. The term ‘biomedicalisation’ is used to describe how medicine has become increasingly technical and techno-scientific (Clarke et al., 2003) and has its roots in the biomedical perception of the body as a machine, favouring drugs and devices to treat problems rather than focusing on changes to the environment (Clark, 2014a). Related to biomedicalisation is the concept of ‘molecularisation’, which ‘envisages life at a molecular level, as a set of intelligible, vital mechanisms among molecular entities that can be identified, isolated, manipulated, mobilized, recombined in new practices of interventions, which are no longer constrained by the apparent normativity of a natural vital order’ (Rose, 2009).

In recent times ‘pharmaceuticalisation’ has been recognised as a separate, albeit overlapping process and concept to medicalisation. Williams et al. (2011) define pharmaceuticalisation as ‘the translation or transformation of human conditions, capabilities and capacities into opportunities for pharmaceutical intervention’ or the ‘redefinition and reconstruction of health problems as having a pharmaceutical solution’ (Williams et al., 2011). The term was introduced in anthropology by Nichter (1989) and in sociology by Williams et al. (2008). Pharmaceuticalisation, like medicalisation, should be considered a value-neutral term, as it may represent both gains or losses to society (Williams et al., 2011). Prescribing medicines has become a dominant, if not the dominant, form of health care in western societies (Busfield, 2010). Pharmaceuticals play a role in the social transformation of society whereby a ‘pharmaceutical regime’ creates a perspective or influences how people think about and deal with the issues of health, nature and identity (Collin, 2016).

### **2.3.1 Early Writers and the Development of the Concept**

The concept of medicalisation first gained prominence in critiques of psychiatry, such as in the work of Barbara Wootton, who in 1956 explored how mental illness was no longer considered to refer to those who were ‘undeniably mad’, but to those ‘who are simply unable to manage their lives’ (Wootton, 1956 cited in Davis, 2006). This shifting of the boundaries represented ‘a steady encroachment of medical science’, she contended. Noting that it was ‘easier to put up a clinic than to pull down a slum’ she identified one

the key arguments of the medicalisation thesis; by employing a reductionist view centred on the individual we are at risk of ignoring the social, cultural, psychological and environmental contexts of health and illness (Clark, 2014a). Szasz, a contemporary of Wootton, also focused on the expansion of psychiatry, whereby problems of living were redefined under the gaze of physicians' own moral judgments as psychopathology. He contended that this 'conquest' by psychiatry and its associated modern, bureaucratic and scientific-technological perspective 'diminishes a man as a person and oppresses him as a citizen' (Szasz, 1991, p.5). In his polemic work, *Schizophrenia: The Sacred Symbol of Psychiatry*, Szasz (1988) accuses the founding fathers of psychiatry of redefining the criterion of disease from histopathology to psychopathology, that is from 'abnormal bodily structure to abnormal personal behavior' (Szasz, 1988, p.312). Both Szasz (1961) and his contemporary Laing (1961) argued that the western medical professional had been given the authority to decide what was normal and abnormal in terms of feelings and behaviours and could decide to classify these as pathological and therefore needing treatment.

This initial consideration of psychiatry as the locus of the process of medicalisation was widened by writers such as Eliot Freidson and Irving Zola in the late 1960s and came to include the whole field of medicine. In many of these early analyses, the medical profession was seen to be central to understanding medicalisation, none more so than that by Ivan Illich in his seminal 1975 book *Medical Nemesis*, which described the 'epidemic of modern medicine' (Illich, 1974, p.15). Illich contended that the environment is the primary determinant of health but that 'awe inspiring medical technology has combined with egalitarian rhetoric to create the dangerous delusion that contemporary medicine is highly effective' (Illich, 1974, p.19). While acknowledging that some medical procedures have become effective, the opening sentence described clearly his position: 'The medical establishment has become a major threat to health' (Illich, 1974, p.11). By 1983 Zola was describing medicalisation as 'the process whereby more and more of everyday life has come under medical dominion, influence and supervision' (Zola, 1983, p.295). Although Peter Conrad had described medicalisation in 1975 as 'defining behavior as a medical problem or illness and mandating or licensing the medical profession to provide some sort of treatment for it', he later went on to deemphasise the role of the medical profession in the process, stating that it is:

a sociocultural process, which may or may not involve the medical profession... The interest of medicalization has predominantly focused on previously non-medical problems that have been medicalized (and often thought to be inappropriately medicalized) ... but actually medicalization must include all problems that come to be defined in medical terms (Conrad, 1992).

### **2.3.2 The Process of Medicalisation**

In the 1960s, writers such as Zola began to consider how the jurisdiction of medicine had expanded and how it was increasingly involved in the management of society, comparable to the more traditional institutions that controlled peoples' lives; 'medicine is a moral enterprise like law and religion seeking to uncover and control things it considers undesirable' (Zola, 1983, p.208). Zola argued that medicine was becoming 'the new repository of truth, the place often absolute and final judgements are made by supposedly morally neutral and objective experts' (Zola, 1972). Although Zola asserted that people themselves were not simply the victims of medicalisation, but were active agents in the process, it was argued that for this control to manifest, people had to subscribe to a certain conceptualisation of the body that was becoming increasingly biomedical (Riessman, 1983, Conrad, 1975). In other words, society in general and individuals must produce and agree on 'technoscientific identities' (Clarke et al., 2003). Thus, issues of power and control are central to theories of medicalisation. A related concept is that of 'governmentality', as theorised by the French philosopher Michel Foucault. Governmentality refers to a system of power that regulates and controls society through the adoption of belief systems shaped by political and social norms; these belief systems become the dominant 'regime of truth' of the time (Wilson and Prior, 2017). Within the context of medicine, issues must first present themselves to the medical 'gaze' (Foucault, 2002, p.ix) and must be defined and constructed as medical problems requiring a medical solution (Williams et al., 2011). In other words, disease experiences are shaped not just by pathologies, but by 'culturally, spatially and historically specific ... disease regimes' (Klawiter, 2004).

The first step in the medicalisation process is to identify a problem that needs a solution; the next is finding a medical solution that suits. Here we return to the fundamental

argument of governmentality by Foucault, that the principal technology of power is ‘the gaze’ (Foucault, 2002, p.ix). By this he means that by turning attention to a matter, by problemising, and by then gathering information on the matter, one informs and creates a type of discourse (Foucault, 1980 cited in Fox, 1997). In other words, as described by Bacchi and Goodwin (2016) ‘that which we propose to do about something indicates what we think needs to change and hence what we think the problem is’. The process of medicalisation relies firstly on beginning to use a medical vocabulary and ideology to order or define a problem, that is, it occurs on a conceptual level (Halfmann, 2011, Jacob et al., 2014). Secondly, biomedical facts come to be accepted (Zola, 1972), and a medical solution to that problem is proposed and endorsed. Simply having a drug to treat a condition can stabilise the notion of the disease itself (Pollock and Jones, 2015) and, in some cases, the drug may become central to the definition of disease categories (Greene, 2007). Eborall and Will (2011) assert that a well-known drug which people believe will do them good develops a ‘special ordinariness’, allows people to present themselves as responsible and legitimises the taking of the medicine. A clear explanation of this is provided by (Parry, 2003) in the trade magazine ‘Medical Marketing and Media’, in an article entitled ‘The Art of Branding a Condition’:

The idea behind ‘condition branding’ is relatively simple: If you define a particular condition and its associated symptoms in the minds of physicians and patients, you can also predicate the best treatment for that condition (Parry, 2003).

An early example of this was the rebranding of Listerine in the 1920s. The product was being marketed for a wide variety of conditions but sales were low. Parry explained that ‘(b)y creating awareness – and anxiety – around an unpleasant symptom that can be framed as a serious sounding medical condition: “halitosis” ... saw sales increase from \$100,000 to \$4million over the next six years and helped make halitosis a household word’. This example, shows how, according to Parry, a company can elevate a benign notion of bad breathe into a serious and ‘risk-affirming’ condition (Parry, 2003). In order to achieve that aim the:

(s)eed(s) must be sown in a complex landscape of audiences involving pharmaceutical companies, external thought leaders, support groups and consumers; and the effort must be coordinated with multiple communications agencies in the fields of branding, advertising, education and public relations ... focused on a single story with a lock and key problem/solution structure (Parry, 2003).

Arguably, the prevailing authoritative discourse in modern medical thinking is preventative health, and specifically the management of risk, so much so that 'the experience of being at risk for disease has been converging with the experience of disease itself' (Aronowitz, 2009). Many healthy people with no symptoms of disease perceptible either to themselves or their doctors receive a diagnosis of disease. These types of disease have no relationship with symptoms but are connected to a statistical likelihood of developing symptoms at some point in the future. Usually such patients are advised to change their lifestyle in order to reduce that risk, but for many people such a diagnosis leads to the prescription of a drug (Greene, 2007). The accepted paradigm of prevention assumes that a greater understanding of biochemistry has improved knowledge of disease precursors, which may then be legitimately medicated, thereby preventing future disease from developing or progressing (Busfield, 2010). Preventative medicine can be primary, secondary or tertiary. Primary prevention refers to preventing a disease before it develops and can be aimed at whole communities or the individual person. Secondary prevention consists of preventing a recurrence of a disease or injury that has already occurred or diagnosing it early to enable early intervention, while tertiary prevention refers to interventions aimed at improving treatment and recovery from an illness or injury (World Health Organization, 2018a).

Preventative health grew out of the State's intervention during epidemics of contagious disease such as leprosy or plague and in its early days was synonymous with 'medical policing' (Skrabanek, 1990). In the nineteenth century, for example, doctors screened prostitutes for the protection of their clients. Insurance companies, armies and employers, in order to 'separate the healthy and useful from the weak and useless', used screening (Skrabanek, 1990). At the turn of the twentieth century, infectious disease accounted for a large proportion of deaths, particularly in cities. In 1900, for example, 44% of deaths

in American cities were due to infectious diseases. The subsequent decline in deaths from infectious disease has been attributed to large scale public health interventions such as clean water technologies, sanitation and refuse management, as well as nutritional gains and economic advances (Cutler and Miller, 2005). According to (Skolbekken, 1995):

(n)ature may no longer be the main reason for risks to our health ... The risk acceptance that is internalized as a fatalistic attitude to these matters is being replaced by an ideology whose primary goal is to gain control over life and death, where identification of and the struggle to reduce/eliminate risk factors have become activities of considerable importance and prestige within the health professionals.

The process of medicalisation has resulted in healthy individuals who have risk factors for a particular disease being subject to more surveillance ‘and the risk state has become more embodied ... more disease-like’ (Aronowitz, 2009). For example, although high cholesterol is only one of several risk factors that *may* contribute to heart disease, it may be reified and evaluated as a current problem, an adverse event in its own right (Heyman et al., 2012). Skolbekken (1995) described a ‘risk epidemic’, a term he justifies through his examination of the rise in the number of published articles in medical journals using the term risk over a period of time. The origin of the risk epidemic may be the current statistical paradigm of scientific medicine and various tools from which it originated. These tools include: the development of scientific thinking to include the concepts of risk and uncertainty as potential sites for medical intervention; the use of risk calculations; the introduction of randomised control trials and clinical epidemiology, and, the development of risk analysis. However, returning to the concept of governmentality, overarching all of these tools and techniques is an ‘ideological background wherein the application of these techniques become legitimate’ (Skolbekken, 1995).

Also of relevance here are surrogate endpoints, defined as ‘biomarkers intended to substitute for a clinical endpoint...[that are]...expected to predict a clinical benefit (or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence’ (Institute of Medicine, 2010). Many clinical interventions now base their evidence of efficacy on their impact on surrogate endpoints rather than symptoms, or

‘hard’ outcomes. For example, in the case of diabetes, concentrations of glycated haemoglobin (HbA<sub>1c</sub>) are used as surrogate markers for outcomes that are important to patients, such as blindness or amputation (Yudkin et al., 2011). These markers may be true risk factors, preclinical manifestations or ‘bystanders without an active role’ (Yudkin et al., 2011). However, markers may take on an existence of their own as new disease entities. Yudkin and Montori (2014) contend that defining blood concentrations that lie above normal but below that defined for diabetes as ‘pre-diabetes’ has little relevance or benefits for clinical practice. In contrast, others have argued that lifestyle interventions in those diagnosed as pre-diabetic may decrease the risk of pre-diabetes progressing to diabetes (Tuso, 2014). To intervene in this way *requires* the diagnosis of pre-diabetes.

Other examples of commonly measured surrogates that can, but don’t always, lie in the causal pathways for disease process include elevated low-density lipoprotein (LDL) cholesterol, blood pressure, albumin excretion rates and C reactive protein concentrations, all of which may be associated with the development of cardiovascular disease (Yudkin et al., 2011). These numbers, or biometric parameters, will by their nature be distributed along a continuum where one extreme represents a level of abnormality that justifies treatment and there has been considerable ‘shifting (of) the demarcation point into the territory previously considered normal’ (Heath, 2013). The strong focus on ‘knowing your numbers’ (Moynihan, 2011), the transformation of risk into disease and the management of risk are key characteristics of 21<sup>st</sup> century medicine. Many physicians and patients may now equate having a risk factor with having a disease (Kreiner and Hunt, 2014), and some have argued that health has come to be defined as risk reduction (Dumit, 2012). This focus on specific ‘risky’ surrogate outcomes has enabled the expansion of disease definitions, whereby thresholds for treatment, such as in the example of pre-diabetes, may be pushed further and further down, thereby expanding the number of people eligible for treatment. Conditions such as high blood pressure, depression, menopause, attention deficit disorder, high blood pressure, pre-menstrual dysphoric disorder, social anxiety disorder, osteoporosis, irritable bowel syndrome and female sexual dysfunction are ‘among those conditions that have either been “created” ... or at least exaggerated by pharmaceutical companies in an extraordinarily successful attempt to sell more drugs’ (Parsons, 2007). While clearly there are people who suffer seriously from such conditions, the central thesis of ‘disease

mongering' is that mild cases are subject to being treated as if they were serious (Parsons, 2007). This process has been described by (Moynihan and Cassels, 2006, p.xiv) in their seminal book *Selling Sickness* as the process by which 'the boundaries that define disease are pushed out as widely as they can be, by contrast, the causes of these supposed epidemics are portrayed as narrowly as possible'. Again, it is important to point out that acceptance of 'risk as disease', the validity of surrogate endpoints, or the expansion of disease definitions, would not be possible without an acceptance of the 'truth claims of biomedicine' (Lupton, 2012, p.12).

### **2.3.3 The Main Actors**

As I have discussed, the process of medicalisation relies, on the conceptual level, on firstly acquiring a medical vocabulary and ideology to order or define a problem as medical (Halfmann, 2011, Jacob et al., 2014), and secondly, on the acceptance of biomedical facts (Zola, 1972). Here I briefly discuss how each of several actors in this process are described in the medicalisation literature. These are: the pharmaceutical industry; the medical profession; patients as consumers; media and marketeers; and government and regulators. Separating these as if they were discrete players within the process of medicalisation is of course useful merely for analytical purposes; in reality each interacts with the other, reinforces the others' position or disrupts it. Ultimately, it is these interactions, rather than the actions of any one type of actor that creates the prevailing, consensual regimes of truth (Kiely and Meade, 2018) required for medicalisation to occur. In Chapter 5, I examine in greater detail the impact of clinical guidelines in this context. These, it is argued, are 'heavily politicised blueprints' of health which identify areas of health requiring governance (Wilson and Prior, 2017), or 'technologies of government' (Edwards and Fernández, 2017). I will return to more detailed analyses of patients and doctors in the context of CVD prevention in Chapter 6, and also present some further consideration of the influence of the pharmaceutical industry and regulation, including clinical guidelines.

#### *The Pharmaceutical Industry*

Clearly, the pharmaceutical industry has an interest in maximising profits, and one way of doing so is by increasing drug use. Some authors have argued that this incentive encourages the promotion of drug use beyond legitimate health needs (Moynihan and

Cassels, 2006, Conrad, 2005) and have termed this process a ‘generation of wants’ (Busfield, 2010, p.935). The strategies for increasing drug sales include marketing and promotion, industry’s control over the process of development of new drugs, and the construction of new medical conditions (Busfield, 2010). Of note to this thesis is the idea that drug companies identify conditions that will require long-term treatment, these being of particular value to future sales. This includes preventative medicine, such as statins for primary prevention of CVD. Busfield (2010, p.937) modifies Ivan Illich’s (1974) dictum that ‘doctors gain legal power to create the need that by law, they alone can satisfy’ and suggests that ‘pharmaceutical companies create health needs that they alone can satisfy’. In Section 2.4, I detail the influence of the pharmaceutical industry within the context of the development of statins and the clinical guidelines governing their use.

### *The Medical Profession*

From the earliest writing on medicalisation, the medical profession has been central to the medicalisation debate and it has been argued that the western medical professional has assumed a privileged position in the definition of normality, the classification of the pathological and prescription of treatment (Szasz, 1961, Laing, 1961, Illich, 1974). Freidson (1970, p.251) worried that ‘(o)nce official jurisdiction is gained, the profession is then prone to create its own specialised notions of what it is that shall be called disease’. Illich described doctors as a disabling profession who had ‘the power ... to ... generate demands for their services and commodities, making individuals increasingly disabled and dependent on professional guidance’ (Radelet, 1978, p.369). As described in the description of the medicalisation process, people conceptualise problems within a progressively technically complex biomedical world and therefore increasingly rely on experts to define health and ill-health. This enables expert doctors, particularly in the field of research, to enact ‘medical imperialism’ (Conrad, 2007, p.9), whereby they extend the domain of medicine (Busfield, 2010).

Allied with this is the concept of medical interventionism, described as the situation where the aim of the medical practitioner is ‘not knowledge but action’ (Freidson, 1970, p.168). ‘Action with very little chance of success is to be preferred over no action at all’ and this can encourage doctors to want to intervene (Busfield, 2010), even when there is little to be gained from the intervention. In the context of prescribing behaviour, GPs

may perceive pressure from colleagues or patients to prescribe for a particular condition (Rashidian and Russell, 2011, Busfield, 2010) or may feel societal expectations to prescribe in a certain way (Tušek-Bunc et al., 2010). A prescriber's knowledge of treatment outcome determines the choices they make in prescribing only in part (Van der Geest et al., 1996), as doctors may use routines or simplified strategies learned or copied from others rather than consciously deliberated. Thus, 'therapeutic traditions' can influence doctors' prescribing (Ohlsson et al., 2005, Nixon and Kousgaard, 2016) and once a product has become part of a doctor's 'personal formulary', it has a propensity to be prescribed routinely through habit 'rather than through any active problem solving approach' (Tušek-Bunc et al., 2010). In addition, doctors have reported that limitations in the time they spend with patients may lead to less than optimal health care (O'Brien Cherry et al., 2012), and arguably a propensity to prescribe by rote. By prescribing, a doctor expresses his or her concern and an acknowledgement of a patient's suffering, and prescribing may be:

... as much a matter of the doctor solving his own problems as solving those of the patient. The doctor's problems are: how to react satisfactorily to the patient's request, how to conceal his uncertainty about cause and cure of the sickness, and how to dispose of the patient in an acceptable manner. The prescription comes to his rescue (Van der Geest et al., 1996).

Despite the characterisation of the medical profession by some as 'god-like' (Lupton, 1997a), there is an inherent uncertainty in medicine. Doctors tend to err on the side of treating the patient who may not need it, rather than not treating at all (Hoffmann and Del Mar, 2017, Lin and Redberg, 2015). One aspect of this uncertainty may be to downplay or underestimate the risks involved in taking a medicine (Hoffmann and Del Mar, 2017). Doctors may feel they do not have the technical expertise to evaluate efficacy and effects of drugs (National Audit Office, 2007) and can take their cue from clinical practice guidelines or recommendations or experts in their field.

### *Patients as Consumers*

Increased internet access, disease support groups and patient consumerism have contributed to the democratisation of medical information. Many authors claim there has

been a change in behaviour by people from being passive patients of the medical profession to active, engaged and responsible consumers of medicine, which may fuel medicalisation (Flower, 2004, Nye, 2003). This creation of new identities for people as patients and the mobilisation of patient groups around drugs has meant that patients (consumers) have become increasingly 'knowledgeable reflexive actors' in making decisions around their own healthcare (Williams et al., 2011). It may be the case that people are less tolerant of physical discomfort than in the past and that 'isolated symptoms' have come to be reclassified as disease (Barsky and Borus, 1995). There is an increasing tendency for disease support groups to 'frame pharmaceutical corporations as allies in their quests for better health' (O' Donovan, 2007), thereby identifying a pharmaceutical solution to their problems.

While there has been some debate on whether this amounts to industry capture of these groups, the trend towards consumerism has been largely 'congruent with, rather than a challenge to, the interests of the pharmaceutical industry' (Williams et al., 2011). Doctors are more likely to prescribe if requested by patients (Busfield, 2010). Although direct-to-consumer advertising of prescription drugs is not allowed in the EU, 'disease awareness campaigns' have become a common feature of medical discourse (Moynihan and Henry, 2006). In addition, pharmaceutical sponsorship of patient advocacy groups may have encouraged those groups to be more receptive of pharmaceutical solutions to their medical issues (O' Donovan, 2007, Williams et al., 2011) and to campaign for the inclusion of certain disease-specific drugs in national reimbursement schemes (Shanahan, 2017). Because drug regulatory bodies such as the FDA will only approve a drug to treat a disease, manufacturers make strong efforts to bio-medicalise lifestyle conditions (Fox and Ward, 2008). A 'domestication' of drugs has taken place, because they are available via a home computer and because the marketing of pharmaceuticals often focuses upon private or personal conditions. Various commonly used drugs fall into this definition, to treat such conditions as obesity, erectile dysfunction, shyness, attention deficit hyperactive disorder and alopecia. This has been described as 'consumer legitimation', whereby pharmaceuticals 'become a core element of what goes on in their users kitchens and bedrooms rather than something extraneous' (Fox and Ward, 2008).

### *Media and Marketeers*

For many people, the mass media are an important source of health-related information and represent a form of authority on medical knowledge (Kroll-Smith, 2003). Mediation may drive medicalisation and in particular pharmaceuticalisation, whereby the media and popular culture reframe health problems as having a pharmaceutical solution (Williams et al., 2011). The media may exaggerate the prevalence of some diseases and fail to consider the problem of over-diagnosis (Woloshin and Schwartz, 2006). However, it may also be the case that the media do not create the process of medicalisation, but rather convey and amplify it over time. Techniques within the media of using celebrities to highlight particular health issues, and then point the patient to ‘ask your doctor if drug ‘x’ is right for you’, can create the impression that ‘this condition could happen to anyone thereby ensuring fertile ground for potential market expansion’ (Williams et al., 2011). Conversely, the media can condemn pharmaceutical intervention, ‘oscillating between oppositional extremes of both idealization on the one hand, and demonization on the other’ (Williams et al., 2011).

In the US direct-to-consumer advertising has been shown to influence pharmaceutical sales (Williams et al., 2011). However, DTC advertising is not permitted in Europe and pharmaceutical companies try to counter this restriction by use of ‘disease awareness campaigns’ which are often run in conjunction with government agencies, in what Angell (2005) has described as ‘marketing masquerading as education’. For example, Woloshin and Schwartz (2006) analysed how the drug company GlaxoSmithKline promoted awareness of ‘Restless Leg Syndrome’ following early trial results for the drug ropinirole. The campaign included press releases about presentations at the American Academy of Neurology and a survey, funded by the company, on this ‘common yet under recognized disorder’. The authors reported that the awareness campaign:

... exaggerated the prevalence of disease and the need for treatment, and failed to consider the problems of overdiagnosis. In essence, the media seemed to have been co-opted into the disease-mongering process (Woloshin and Schwartz, 2006).

### *Government and Regulators*

Governments have multifaceted roles to play in access, pricing and the level of medical prescribing. Governments, through health care policies on access and reimbursement, will affect the access to, and thereby the consumption levels of, prescription drugs. For example, Richardson et al. (2014) found that medical card eligibility increased the likelihood of polypharmacy in older adults. It has been argued that health policy in Ireland exhibits key characteristics of ‘neo-liberal governmentality’ (Wilson and Prior, 2017), by repositioning power away from a centralist State to ‘government as a series of agencies, institutions and actors through which power becomes manifest’ (Edwards and Fernández, 2017). Health policy in Ireland has been constructed around a particularly neo-liberal narrative that strongly promotes risk prevention by the individual, and doctors are delegated ‘power and responsibility for population health’ (Wilson and Prior, 2017) and strategic health policies are part of the ‘discourse coalition’. Edwards and Fernández (2017) note the regulatory nature of public health initiatives. For example, in 1998 the Minister for Health and Children in Ireland established the Cardiovascular Health Strategy Group, which published the ‘Building Healthier Hearts – Report of the Cardiovascular Health Strategy Team’. This report did not recommend risk assessment or ‘screening’ for whole groups of the population but rather a combination of ‘opportunistic and systematic risk assessment, with a very structured approach to the management of those identified as being at high risk’ (Department of Health & Children, 1999, p.70). However, a new National Cardiovascular Health Policy (2010–2019) was published in 2010. That Policy suggested a shift in emphasis from those at high risk of CVD to a whole population approach, noting:

Effective prevention requires a shift of the entire distribution of a risk factor (e.g. raised cholesterol) to lower values. It should extend beyond a focus on high-risk individuals, utilising cholesterol-lowering therapies, to population-based approaches, preventing the development of the risk factors themselves (Department of Health & Children, 2010, p.2).

I will return to the influence of policy documents such as health strategies, as well as clinical guidelines and medical journals, on doctors in more detail in Chapter 7.

Governments can regulate approval of medicines, though this role is increasingly taken over by cross-national bodies such as the European Medicines Agency (EMA). Agencies such as EMA and the Food and Drug Administration (FDA) in the US have been criticised for having a strong interest in supporting the pharmaceutical industry. Perverse incentives for the regulatory bodies exist because of their reliance on fees from industry for funding, as well as increased competition between agencies to license new drugs (Boardman and Heeley, 2015, Health Action International, 2015). There have been concerns raised about the effect of the changing forms of governance of industry (Williams et al., 2011, Busfield, 2010) and there is some evidence of corporate bias of, and privileged access to, regulatory bodies by pharmaceutical companies (Abraham, 2010). Hogarth (2015) describes this shift from gate-keeper to a more collaborative role with industry by the FDA, and says that this ‘neo-liberal corporate bias’ was justified by ‘the assumption that the interests of patients are aligned with those of industry’.

#### **2.3.4 Critiques of the Medicalisation Literature**

The medicalisation thesis is not without its critics. Greene (2007), for example, dismissed the over simplification of the process of medicalisation which he describes as a ‘paranoid polemic describing an omnipotent medical profession constantly seeking to expand its province over the healthy’ (Greene, 2007, p.5). Nor is it, in his opinion, simply clever marketing on behalf of the pharmaceutical industry, which generates new disease categories. It is rather ‘an overdetermined process that illustrates the porous relationship between the science and the business of health care and the centrality of disease categories in contemporary conceptions of health’ (Greene, 2007, p.5). However, I argue that Green misrepresents the medicalisation literature as polemic. Other writers, such as Illich (1974), have been at pains to point out the multi-layered, complex nature of the process; a process that requires the engagement of many sectors of society, not simply an ‘omnipotent’ medical profession and a ruthless pharmaceutical industry. Later in this chapter I will chart the medicalisation of preventative cardiovascular health based on his book *Prescribing by Numbers* (Greene, 2007). Despite the fact that Greene does not use the term ‘medicalisation’, his book in fact illustrates the classic multisectorial trajectory of medicalisation in this context.

As noted, some of the earliest writers on medicalisation focused on the practice of psychiatry. While much of that debate has remained polarised (Whitaker, 2005), some authors have welcomed criticisms of the practice of psychiatry. For example, responding to the critiques of writers such as Szasz and Laing, as outlined earlier, the contemporary psychiatrist Desai (2005) notes that the ‘larger conceptual and ideological opposition of antipsychiatry to the practice of psychiatry at the macro level have been remarkable in the development and refinement of psychiatry’. This refinement has included a recognition that there is a spectrum of mental illness, varying from the mild to severe, even in the case of schizophrenia, and that a combination of types of interventions, ranging from pharmacological to social may be appropriate depending on the individual patient (Chien and Yip, 2013).

The term disease mongering is, according to Doran and Henry (2008) ‘adequate for labelling obvious egregious practices... it is good for shaming the mongers’ but it is limited in expressing the complexities involved in its emergence. Ghaemi (2006) takes exception, in particular, with the inclusion of bipolar disorder as a disease which has been ‘mongered’. He writes that the condition has been well described since antiquity and in order to accept the suppositions of disease mongering, ‘one would have to suppose that Arataeus of Cappadocia was heavily influenced by the pharmaceutical industry in the 1<sup>st</sup> century AD!’. Some critics point out that some activities classified as nefarious, such as disease awareness campaigns, can be legitimate and beneficial (Doran and Henry, 2008). For some, because funding for public health projects is often scarce, commercially sponsored campaigns are often welcome and valuable. Doran and Henry cite the commonly described examples of disease mongering such as mild depression, social anxiety disorder, attention deficit disorder, irritable bowel syndrome, restless legs, erectile dysfunction and female sexual dysfunction. While all these conditions exist, they usually represent a broad spectrum in terms of symptom severity and frequency in the individual, which may not justify its pathologisation or the use of a drug to treat it. I argue, however, that many of these criticisms could be set aside by simply using the term medicalisation as value-neutral and by accepting that the legitimacy of claims of medical territory can only be established by careful examination of the diagnostic categories which have come to be reclassified as medical. In addition, within these categories there may be individuals who benefit from medicalisation while others do not, and individuals

whose preferences and goals differ from others. Disentangling these dilemmas in the context of CVD prevention is the fundamental aim of this thesis.

The critiques outlined above are largely arguments of etymology; concerned with the meanings and implications of words. The second criticism I present concerns the *effects* of medicalisation. Medicalisation has been described as a process that involves the application of this biomedical model characterised by reductionism and individualism (Clark, 2014a). Reductionism downplays context and ‘reduces explanations for problems to the physical realm, overlooking social, cultural, psychological or environmental factors’. The complexity, relativity and experiences of health are excluded and both causes and solutions of problems are sought in biology rather than in the social or political realms. In recent times, there have been calls for Universal Health Coverage (UHC) in many countries and UHC is one of the stated aims of the World Health Organization’s Sustainable Development Goals (World Health Organization, 2018b). However, concerns have been voiced as to whether UHC conflates health with health care and whether these goals are reductionist because they focus on:

... preventative and curative actions delivered at the individual level and ignore the social and political determinants of health...UHC risks commodifying health care which threatens the underlying principles of UHC of equity in access and of health care as a collective good (Clark, 2014b).

Individualism places the responsibility for problems on the individual rather than on the structures that shape that individual’s experience and can deflect attention away from collective and state role or responsibility. For example, Global Health Watch 3 criticised the current healthcare research paradigm that ‘is heavily skewed in favour of biomedical interventions, to the almost complete neglect of research on health systems and the social determinants of health’ (People's Health Movement et al., 2011). In the context of CVD prevention, the problem with the construction of the individual as the sole focus of risk is that the socio-economic determinants of health in neo-liberal Ireland and similar countries may become obscured. Rockhill (2001) has noted that people in the lower socio-economic strata may be less likely to comprehend the arithmetic behind risk

information, or have the psychological, social and economic resources needed to alter the factors contributing to their ‘personal risk’.

## 2.4 Medicalisation and Statins

As noted above, some of the earliest writings on medicalisation were largely situated within the realm of mental illness and considered physicians to be central to the process. More recent writings have expanded to the ‘pathologization of everything’ (Conrad, 2007). For example, the availability and thresholds of medical interventions have changed what is considered to be normal ageing (Kaufman et al., 2004) and when it is acceptable to die. Conrad states that:

Difference in learning styles have become learning disabilities ... divergences in sexual desires ... have become sexual dysfunctions ... We have long turned normal human events into medical events ... conception to childbirth to menopause ... Virtually any human difference is susceptible to being considered a form of pathology (Conrad, 2007, p.163).

Whether medicalisation can be considered positive or constitutes the overuse of medicine depends on the context and there have been calls for the examination of the process on a case-by-case basis (Carter et al., 2015). It is to this call that this thesis responds. In this section, drawing heavily on the book *Prescribing by Numbers* by Jeremy A. Greene, I chronicle the trajectory of the medicalisation of hyperlipidaemia, and the establishment of statins as a cornerstone of treatment.

As described in Chapter 1, there is no doubt that there has been a large increase in the use of statins since their introduction in the late 1980s, particularly in primary prevention of CVD. Earlier in this chapter I examined the processes and actors involved in medicalisation in general: problemising an issue and having a medical solution for the problem; expanding disease definitions; preventative medicine, risk and surrogate endpoints; governmentality and the hegemony of biomedical discourse. In addition, I identified the main actors that drive medicalisation: the pharmaceutical industry; the medical profession; patients as consumers; the media and marketeers; and government

and regulation. In this section, I build on this and examine statins in the context of some of these drivers and actors.

During the twentieth century, medical attention turned from infectious, acute causes of mortality to chronic diseases, as the burden of disease shifted. Chronic disease had always been there, of course, but had been considered a normal part of ageing and degeneration. With the reduction in mortality from infectious disease, deaths from cancer and heart disease became increasingly the focus of medical attention. Surveys by state bodies in the 1930s quantified the prevalence and severity of various chronic diseases in the US (United States Public Health Service, 1938) and turned attention to the significance of chronic disease as a threat to public health. In an early example of how media attention on a celebrity's health can 'massively (amplify)... coverage about important neglected problems' (Chapman, 2012), the heart attack suffered by President Eisenhower in 1955 and his subsequent recovery led to intense public interest and scrutiny into coronary heart disease (CHD) and its prevention. The germ theory, widely accepted by among mainstream medics by the end of the nineteenth century, paved the way for an understanding of diseases as having a causal, mechanistic, external genesis. If the causal agent could be identified, then clearly containment, prevention and eradication of the disease was a possibility. It became apparent that most heart disease was associated with a hardening of the arteries, atherosclerosis, and researchers began to search for the underlying mechanism that caused this (Greene, 2007, p.153). In the late 1940s the Framingham study, a population-based study to determine the factors associated with development of CHD, was undertaken and the statistical association between cholesterol and CHD was pronounced in 1957.

Thus, the new focus on the 'risky' surrogate endpoint of raised cholesterol was accepted at a conceptual level as a legitimate medical measurement. By the early 1960s, the problematisation of high cholesterol was complete; it was 'a highly visible target awaiting its magic bullet' (Greene, 2007, p.157). The next step in the medicalisation process was to identify a medical solution, thus creating a space for the pharmaceutical industry to fill.

Following the Framingham study, dietary interventions initially became a focus for cholesterol lowering therapies and the view that the high fat, high cholesterol diet was unhealthy became popularised in the US media. This thesis had not been backed by any large-scale studies and attempts were made to set up the large-scale National Diet-Heart Study, but proved methodologically impossible and prohibitively expensive. The subsequent Multiple Risk Factor Intervention Trial (MRFIT) found negligible value in any method of risk reduction and in 1980 a National Academy of Science's Food and Nutrition Board report pointed out that the association between cholesterol and CHD was not proven sufficiently for cholesterol to be considered a treatable condition. Nonetheless, this was an opportunity for the pharmaceutical industry to find a pharmaceutical solution to the cholesterol 'problem'. Initial attempts however, were unsuccessful. The first cholesterol lowering drug was withdrawn due to side effects and others were toxic and unpleasant to take or found not to reduce total or cause-specific mortality (Greene, 2007, pp.157-167). A new trial 'The Lipid Research Clinics Coronary Primary Prevention' trial (LRC-CPPT) using a drug as a proxy for successful dietary reduction of cholesterol reported a 'slim margin of difference' between the placebo and treatment groups (Greene, 2007, p.168). The study included individuals whose only risk factor was high cholesterol, and excluded those with diabetes, hypertension and prior CVD. Although the authors acknowledged that the results could be interpreted to apply only to middle aged men with cholesterol levels over 265mg/L (6.8mmol/L), they recommended the trial's implication be extended to other age groups and women because cholesterol levels and CHD risk are continuous variables. Thus, a medical solution had been identified to the problem of high cholesterol and the expansion of the disease definition to include people outside of the trial's remit began.

As previously outlined, medicalisation involves acceptance of the 'truth claims of western medicine' (Lupton, 2012, p.9) and Greene (2007, p. 168) describes how consensus was 'manufactured' following these less than impressive beginnings to the cholesterol-lowering thesis. The National Heart, Lung, and Blood Institute (NHLBI) organised a 'Consensus Conference' following the publication of the LRC-CPPT trial's results and deemed the study to be 'a solid kernel of truth' (Greene, 2007, p.171). From this, the National Cholesterol Education Program (NCEP) was formed to focus on 'strategies for overcoming barriers to 'cholesterol awareness' in professional and patient

populations' (Greene, 2007, p.172). For professionals, articles were placed in medical journals, educational modules designed for both qualified doctors and students. To reach the public, the NCEP developed posters, brochures, articles for women's magazines and the 'Know Your Number' campaign. Responsibility for the cholesterol education programme included groups such as the American Heart Association, the American Medical Association and the American College of Cardiologists, as well as local and state government departments.

In 1987 the NCEP stated that cholesterol awareness had risen in the two years of the programme's existence, but controversy still existed among physicians who contested the validity of the LRC-CPPT trial and the necessity of the NCEP (Greene, 2007, p.177). For example, one critique noted the heavy reliance at the launch of Mecavor (lovastatin) on a small number of expert investigators who were both researchers of the drug and architects of the NCEP guidelines (Moore, 1989). Another, published by epidemiologist William C. Taylor demonstrated that, even if the LRC-CPPT results were valid, they would add eighteen days to the average American's life 'at significant cost to comfort and pocketbook' (Greene, 2007, p.177). However, the clinical trials and subsequent introduction of two further statins, simvastatin and pravastatin, provided a more 'tightly defensible argument for the value of cholesterol detection and treatment'. By the end of the 1990s, consensus was largely established on the benefits of statins and criticisms confined to 'a conspiratorial feature of the far-left press' (Greene, 2007, p.185-186); the hegemony of biomedical discourse in this context was established. I argue that this consensus exemplifies how particular risks become legitimised and how 'risk should be seen as a joint production of *knowledge* about the future and *consent* about the most desired prospects' (Brown, 2014). Risks without consensus fail to become legitimate.

One month after lovastatin was launched, the NCEP published the first US national guidelines for the detection and treatment of high blood cholesterol. As I have noted, simply having a drug to treat a disease can stabilise the notion of the disease as a legitimate problem requiring treatment (Pollock and Jones, 2015), and Greene (2007, pp.178-190) notes that:

... the expansion and growth of cholesterol treatment guidelines in the late 1980s and 1990s had everything to do with the rise of the statins... Statin trials are probably the most visible example of the hydraulics by which commercial clinical trials now drive the production of clinical guidelines and the standardization of clinical practice.

Data has shown that the distribution of serum cholesterol levels in the general population is normally distributed with the centre of the bell-shaped curve at 195mg/dL, (5 mmol/L) and medical textbooks in the 1950s and 1960s listed 130-260mg/dL (3.36-6.7mmol/L) as a normal range for total cholesterol; values above 300mg/dL (7.8mmol/L) were considered abnormally high (Greene, 2007, pp.195-196). If the population itself was the reference for the normal distribution of cholesterol levels then a statistical definition of abnormal could be applied. However, in 1985 the National Institutes of Health Consensus Conference on Cholesterol and Atherosclerosis shifted these boundaries. Advocates argued that as CHD was correlated with the cholesterol rich American diet, the distribution for this population could not be considered bell-shaped (normal). The threshold delineating normal from abnormal was set at 240mg/dL (6.2mmol/L) and 'the US population was neatly transformed from arbiter of normality to locus of pathology' (Greene, 2007, p.197) and the demarcation point of normality shifted (Heath, 2013). In 1991 Merck launched a Phase V post-marketing study of Mevacor (lovastatin) into the treatment of abnormally high cholesterol levels using these new guideline thresholds. This trial, called EXCEL, was not designed to examine hard cardiovascular endpoints, but rather whether participants receiving the drug achieved the new cholesterol thresholds. The study was a success, as the majority of subjects achieved these levels.

Thus, despite the criticism of some clinicians of the arbitrary nature of these thresholds (Oliver, 1985), the publication of this trial validated both these guidelines and Mevacor. EXCEL, according to Greene validated these new 'guidelines and concretize(d) them into more substantive forms of clinical knowledge, but the second generation of large scale statin trials increasingly came to exert a formative influence on the guidelines themselves' (Greene, 2007, p.203). By 2000 about 35 competitive trials had been conducted comparing the head-to-head effectiveness of one statin compared to another and 'the bodies of clinical trial subjects became a battleground of a brand warfare among

blockbuster cholesterol medications' (Greene, 2007, p.205). Two trials for the secondary prevention of CVD, the Scandinavian Simvastatin Survival Study (4S) and the Cholesterol and Related Events trial (CARE), exerted a strong influence on a revision of the 1997 NCEP guidelines. Both trials had demonstrated that lowering cholesterol resulted in fewer CVD related deaths. The NCEP incorporated these findings and recommended a further lowering of LDL cholesterol levels in those with established CHD. This widening of 'disease threshold' created 'several million additional candidates for statin therapy' (Greene, 2007, p.207) and the success of these trials 'led many to wonder openly if there was indeed any limit to how far those boundaries could be pushed' (Greene, 2007, pp.210-211).

Following the development of Mevacor, the European Atherosclerosis Society issued its first policy statement on strategies for the prevention of CHD (European Atherosclerosis Society, 1987). In 1994, a Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension published joint recommendations on the prevention of CHD (Pyörälä et al., 1994). The American Heart Association joint statement was issued the same year and endorsed by the American College of Cardiology. The subsequent publication of major trials such as 4S, CARE, LIPID, AFCAPS/TexCAPS, WOSCOPS, and PROVE-IT, showing the benefits of lowering cholesterol on cardiovascular outcomes, provoked further revisions of clinical guidelines by both the American and European societies. The European guidelines were again updated in 1994, 1998, 2004, 2007, 2012 and 2016. Apart from the most recent guidelines in 2016, each subsequent European guideline has lowered treatment thresholds for both those with and without CVD. In Chapter 5 I examine the implications of these changing clinical guidelines in more detail.

To conclude this section, the history of the development of statins has been intricately bound with the medicalisation of high cholesterol. I have outlined how the 'problem' of high cholesterol was defined as a disease demonstrating the 'fluid contemporary boundaries between physiology and pathology' (Greene, 2007, p. 218), as well as the establishment of a surrogate endpoint as a disease in its own right. I outlined how a medical solution for that problem, identified in the form of statins, and how the hegemony of biomedical discourse, particularly concerning preventative health and risk,

was established and reinforced by the publication of trials and simultaneous development of clinical guidelines, all hallmarks of the processes of medicalisation. Medicalisation, according to (Clark, 2014a), has a reproductive or escalating aspect; once defined in medical terms, especially if done so by powerful institutions, problems and solutions may be repeatedly framed as such over time and thus reinforced. Finally, I demonstrated how the lowering of thresholds for treatment has drastically increased the numbers of ‘candidates’ for treatment; a discussion I will return to in Chapter 5. In addition, I identified how the main actors, the pharmaceutical industry, the medical profession, the media and marketeers, and the regulatory influence of clinical guidelines, have driven medicalisation in this context.

## **2.5 Medicalisation and Overdiagnosis – The Boundaries**

*‘What is too much medicine and who gets to decide?’*

Macdonald and Loder, 2015

As we have seen, medicalisation has been defined as a process by which some problem not previously considered to be medical is now dealt with in the medical realm. Medicalisation is a value neutral term, and the process can represent either net benefit or net loss to society. However, the term is used by many writers pejoratively; to be medicalised is a bad thing and represents an unwarranted expansion whereby healthy people are now considered sick. It is related to, but not the same as, the concept of overdiagnosis. Overdiagnosis can be defined as the diagnosis of a condition, which, if undetected would not have caused symptoms or death (Hofmann, 2016b). Both medicalisation and overdiagnosis are shrouded in uncertainty. In the case of medicalisation, the uncertainty lies in the legitimacy of the medical claim on a condition or whether ‘extension of medical authority (goes) beyond a *legitimate* boundary’ (Hofmann, 2016a) (my emphasis), or has ‘proceeded too far’ (Busfield, 2015). In overdiagnosis, on the other hand, the uncertainty lies in whether or not the diagnosis will do good or harm; ‘its definitions presuppose prophetic abilities’ (Hofmann, 2016b). Who ‘gets to decide’ the legitimacy of this boundary inevitably depends on the current ‘regime of truth’ that is accepted by society; a theme I return to in Chapters 7 and in the concluding chapter of this thesis. While both medicalisation and overdiagnosis consist of

expansion of the concept of disease, in overdiagnosis the phenomenon has *already* been described in biomedical terms, whereas in medicalisation previously non-medical phenomena have come to be described in biomedical ways and are given medical significance. The two concepts are mutually reinforcing. Medicalisation influences overdiagnosis in how health and disease are defined at the macro level, while simultaneously medicalisation follows overdiagnosis in the doctor's surgery at the micro level (van Diik et al., 2016).

The need to assess the overuse of medicine has been recognised by the World Health Organisation (WHO) (World Health Organization, 1987) who examined the 'rational use of medicine' and found that worldwide more than 50% of all medicines are prescribed, dispensed or sold inappropriately. However, the WHO did not advise on how to assess where thresholds of clinical need should be set. In recent years debate on overdiagnosis has 'escaped the closed rooms of professionals and societies... to become a broader ideological critique of excessive medicine' (Hofmann, 2016b). Medical journals such as *The BMJ* and the *Journal of the American Medical Association* have highlighted the problems of what they describe as *Too Much Medicine* and *Less is More* respectively. Campaigns such as Choosing Wisely have been launched to encourage 'discussion between clinicians and patients about the need, or lack thereof, for many frequently ordered tests or treatments' (Cassel and Guest, 2012). Central to this debate has been the challenge of how to define and circumscribe overdiagnosis, which means different things to different people. This dilemma highlights the moral and cultural dimensions of medicine, throwing up questions that more clinical data cannot answer. When to intervene is a moral consideration as is the question of when to stop intervening, and we:

... quickly confront moral considerations, such as what type of benefit or harm should matter; how different benefits or harms, or benefits or harms to different people, should be weighted; whether benefits and harms should be measured in individuals or systems and society; and who should judge which benefits and harms matter (Carter et al., 2015).

The various concepts related to overdiagnosis may be disentangled to some extent but some definitions are broad, some narrow and that many interact and influence each other.

Overdiagnosis, overdetection, false positive, misdiagnosis, overtreatment, overutilization, expanded disease definitions, disease mongering, and overmedicalisation all are considered related to overdiagnosis (Carter et al., 2015). It has been suggested that the use of an overarching term of ‘too much medicine’ is ‘arresting, inclusive and easy to understand’ (Carter et al., 2015). However, what ‘too much medicine’ means will vary according to the condition being examined and an appropriate analytical method for each condition would be useful. For each condition, the drivers of overdiagnosis and potential sources of bias may differ and there is still disagreement about how to analyse overdiagnosis. This may be exacerbated by deeply held values that support people’s understandings of health and medicine, in other words value judgements are inherent to the concept of overdiagnosis (Hofmann, 2016b). Such value judgements can vary significantly from person to person and it is difficult to quantify exactly where the thresholds of overdiagnosis lie from the perspective of the individual. For example, Albarqouni et al. (2017) conducted a systematic review of evidence regarding the minimum acceptable risk reduction of a cardiovascular event which patients feel would justify daily intake of a preventative medication. The review reported that while an average of 60% of participants would take a medication with an NNT of >30%, the range of preferences reported in included studies ranged from 31% to 81% (Albarqouni et al., 2017). The authors concluded that guidelines and clinical consultations should account for these average and individual values in setting risk thresholds. The concept of shared-decision-making (SDM), as opposed to doctors making decisions for patients, has become increasingly prominent in health care policy and practice (Elwyn et al., 2012) and is central to the dilemma of establishing the boundaries of overdiagnosis. It is a topic I return to in Chapter 8.

Finally, Klawiter (2004) argues that ‘experiences of disease are shaped not only by the individual circumstances of the disease sufferers and the particular character of their pathologies, but by culturally, spatially and historically specific regimes of practices’. Inevitably, however, the power relations manifest in regimes of truth, such as in the prevailing biomedical model, cannot be bracketed out when trying to determine what *appropriate* medical intervention might consist of. I also return to this dilemma in Chapter 8.

## 2.6 Conclusion

In this chapter I have outlined the basic concept of medicalisation and other related and overlapping concepts such as bio-medicalisation, molecularisation, pharmaceuticalisation and overdiagnosis. I described how the process of medicalisation occurs first through the recognition of a problem and secondly through having or finding a medical solution to that problem. In this way, medicalisation is strongly related to governmentality; that is, the way in which society is shaped by powerful regimes of truth that define which ways of thinking and which ways of behaving are legitimate. This is not a system of truth imposed on society, rather it is a broad consensual acceptance by society that this way of thinking and behaving in this context is correct. I identified several actors in the context of medicine who influence this regime of truth including the pharmaceutical industry, the medical profession, patients, media and marketeers and government and regulators. I also described how the history of the development of the concept of hypercholesterolaemia and the development of statins can be understood with reference to the process of medicalisation.

Although the pejorative use of the term medicalisation by other writers is not without its critics, throughout my thesis I use the term medicalisation in a neutral way. I understand it to simply mean that something has moved into the medical realm. I have noted the closely aligned concept of pharmaceuticalisation and considered whether this word, in fact, better encapsulates the central argument of my thesis. However, I contend that more freedom is afforded in my analyses by using the word medicalisation, as this allows consideration of pharmaceutical and non-pharmaceutical responses to the problem of hyperlipidaemia. The tricky issue of how to distinguish medicalisation and overdiagnosis has been noted by other writers and this issue, in fact, is at the heart of this thesis: in the context of statins for primary prevention of CVD, *whether* and *in what circumstances* medicalisation of hypercholesterolaemia represents overdiagnosis.

# **3 Cross-sectional Analysis of the Prevalence and Predictors of Statin Utilisation in Ireland with a Focus on Primary Prevention of Cardiovascular Disease**

## **3.1 Introduction**

### **3.1.1 Background**

The last thirty years have seen a large increase in the utilisation of statins (HMG-CoA reductase inhibitors) for the primary and secondary prevention of cardiovascular disease (CVD) (Walley et al., 2005, Feely et al., 2000, Wallach Kildemoes et al., 2008, DeWilde et al., 2003). In Ireland the number of statin patient treatment days per 1,000 inhabitants increased between 2000 and 2003 by 192%, the highest recorded increase in a study of nine European countries (Walley et al., 2005). By 2014, over €50 million was spent annually in Ireland on these medicines in State-funded purchases alone (Health Service Executive, 2014). While the ageing population in developed countries has been cited as a driver of increased utilisation of statins, Wallach Kildemoes found that increasing treatment intensity, rather than population ageing, was almost exclusively responsible for this rise.

Statins may be prescribed for those with known CVD (secondary prevention), diabetes and familial hypercholesterolaemia (primary prevention), as well as for those considered 'at risk' of CVD but who have not yet had an event (primary prevention). The clinical guidelines relevant to the cohort in this study were those of the European Society of Cardiology 2007 (Graham et al., 2007), which recommended that those with established CVD and diabetes be considered as the highest risk group. All others were to be assessed using the SCORE risk assessment tool (Conroy et al., 2003). If a person was found to be above a 5% risk threshold (over ten years) using this method, or if they had established CVD or diabetes, the total cholesterol level recommended was 4.5mmol/L, and/or a low-density lipoprotein level of 2.5mmol/l.

There is some evidence that statins are underused in certain sections of the population (Murphy et al., 2015, Wu et al., 2013, Condliffe et al., 2010, Feely, 1999) and that statins

are not targeted at those most likely to benefit (Teeling et al., 2005, Johansen et al., 2014). However, increases in statin prescribing may be linked to changing clinical guidelines, which have been identified as drivers of a process of medicalisation as they generally widen the definition of disease (Moynihan et al., 2013). Updates of guidelines have included changes to thresholds of blood cholesterol levels and to risk categorisation, which lead to recommendations for statin therapy to expanded numbers of people. In particular, the use of statins in people without previous CVD (primary prevention) has been the subject of controversy (Abramson et al., 2013, Goldacre and Smeeth, 2014). Some authors criticise the extrapolation of clinical guidelines to subgroups, such as women or the elderly (Wallach Kildemoes et al., 2012b), and those with diabetes (Chang et al., 2013), where the evidence of a favourable risk-benefit ratio may not be conclusive. Although some studies have analysed statin use by broad diagnostic groupings (DeWilde et al., 2003, Kitzmiller et al., 2013, Johansen et al., 2014), analysis by diagnostic indication (Wallach Kildemoes et al., 2012a), as well as by ‘at risk’ categorisation, could increase knowledge of drug utilisation patterns. This, in turn, could help explain the drivers of increased utilisation and the extent to which statins are used in patients with lower CVD risk, where the benefits may be limited or where the harms of statins may outweigh those benefits, particularly in primary prevention of CVD (Golomb et al., 2012, Wallach Kildemoes et al., 2015, Goldacre and Smeeth, 2014).

Wallach Kildemoes (Wallach Kildemoes et al., 2012a) constructed a hierarchy of indications for which statins were prescribed (Appendix 1). This hierarchy was based on European Guidelines on prevention of CVD (Graham et al., 2007), the most recent of which, at the time of data collection, were published in 2007. This consisted of eight mutually exclusive levels of markers of CVD-related diagnoses and diabetes. The indication for a person with several of the listed medical conditions was considered to be that which placed them highest on the hierarchy. For example, if a person had both a previous myocardial infarction (MI) *and* hypertension, they were stratified into the MI category, that being the higher-level indication (Appendix 2).

### **3.1.2 Objectives**

The aim of this study was to describe the prevalence of statin utilisation by indication, age and gender, in community-dwelling adults in Ireland aged 50 years and older in the

period 2009-2011, with a focus on primary prevention of CVD. This included an examination of those factors, in particular CVD-related diagnoses based on a hierarchy of indications, which are associated with increased statin utilisation. A secondary analysis was undertaken to examine statin utilisation based on the risk of developing CVD, as measured by the SCORE risk assessment tool.

## **3.2 Methods**

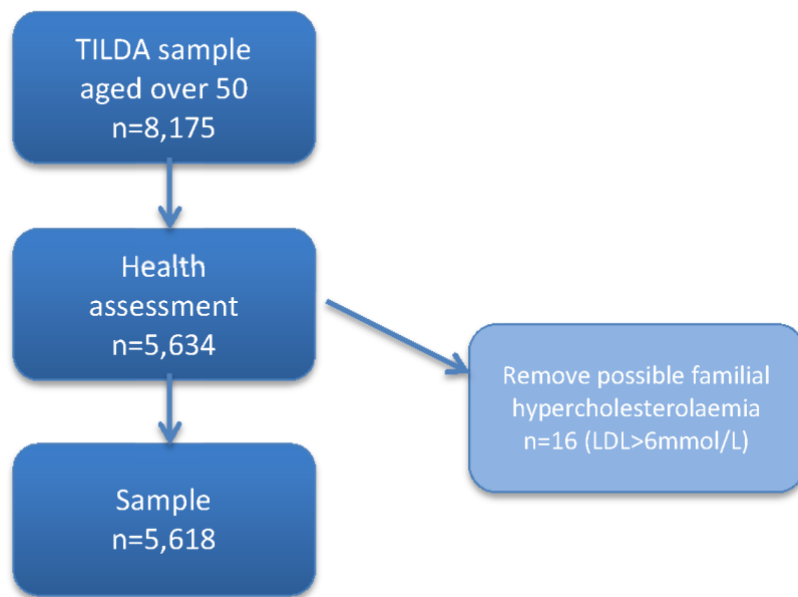
### **3.2.1 Design**

The study used cross-sectional data from Wave 1 (2009-2011) of The Irish Longitudinal Study on Ageing (TILDA). TILDA collects data on a nationally representative sample of community living adults aged 50 years and older in Ireland (Barrett et al., 2011). This allowed us to examine self-reported drug utilisation rather than prescribing data, which may be a more accurate way of assessing drug use. Ethical approval for the TILDA study was received from the Trinity College Research Ethics Committee and all participants provided written informed consent. As my study comprised secondary analysis of TILDA data, which is anonymised, further participant consent or ethical approval was not required.

### **3.2.2 Participants and Setting**

Participants were selected using RAMSAM, a system for drawing a random sample from the Irish geo-directory (Whelan, 1979). Participants took part in a face-to-face computer aided personal interview (CAPI) in their home, followed by a health assessment either in their home or at a designated health centre. Figure 3.1 shows a flowchart of participants included in my analysis. Of the 8,175 individuals within TILDA aged over 50, 5,634 undertook a health assessment. Since diagnosis of familial hypercholesterolaemia was not clear from the data, I removed 16 individuals whose LDL levels were  $>6\text{mmol/L}$  from the sample. This gave a final sample of 5,618 individuals.

Figure 3.1: Flowchart of the Number of Participants Included in the Analysis



Note: LDL= low-density lipoprotein.

### 3.2.3 Variables

A full description of the variables used is presented in Appendix 3.

#### *Statin Use*

Current medication use was recorded directly from respondents and was cross-checked by the interviewer who examined medication labels, which the participant showed them. Good agreement between self-reported prescription medication use and pharmacy dispensing records for this cohort has been reported (Richardson et al., 2013).

#### *Socio-demographic Variables*

Socio-demographic data were collected by TILDA including age, gender and living arrangement. Six categories of both socio-economic status and income levels were described. Educational status was described as ‘Primary or None’, ‘Secondary’ or ‘Third Level or Higher’. Participants were described as living either in Dublin city or environs, in another urban area or in a rural area.

### *Health Care Variables*

Medical insurance status was described as ‘No cover’, ‘Medical insurance’ for those with private medical insurance or ‘Medical card’ for those whose medical costs were covered by the State. I recoded the number of GP visits into five categories – none, 1 to 2, 3 to 4, 5 to 6, and 7 or more. Polypharmacy was recorded in the data as receiving five or more medications (excluding supplements) simultaneously. For the purpose of my analysis I did not include statins as one of the five medications.

### *Indication*

The indication for statin usage was determined during the CAPI. Participants were asked: ‘Has a doctor ever told you that you have any of the following conditions?’ The conditions listed included: high blood pressure or hypertension; angina; a heart attack; congestive heart failure; diabetes or high blood sugar; a stroke; mini-stroke or transient ischaemic attack; high cholesterol; a heart murmur; or any other heart trouble. An indication hierarchy was used as described by Wallach Kildemoes and participants were assigned to the highest level of indication. The categories included in the hierarchy were MI, ischaemic heart disease (IHD), stroke, potential atherosclerotic conditions (PAC), diabetes, hypertension, high cholesterol and none of these conditions (no diagnosis).

## **3.3 Analysis**

The prevalence of statin utilisation was calculated overall and for each age, gender and indication. A multivariable logistic regression model of whether an individual was taking a statin or not was estimated, controlling for cardiovascular indication and socio-demographic factors. This provides, for each covariate, the odds of statin use for one category of the covariate relative to another category, adjusting for all other covariates in the model. In particular, I estimated a stepwise (backward selection) model and applied a 10% significance level for removal. This means that I removed the variable with the greatest p-value, one at a time, until all remaining variables had a p-value less than the 10% threshold. The choice of variables included in the initial model was influenced by the data available in TILDA, as well as previous research, some of which had found significant associations between statin use and educational status (Selmer et al., 2009), gender (Selmer et al., 2009, Kitzmiller et al., 2013, Johansen et al., 2014), age (Norris et al., 2014, DeWilde et al., 2003), socio-economic status (Norris et al., 2014, Kitzmiller et

al., 2013, Wu et al., 2013), number of GP visits (Wu et al., 2013), polypharmacy (Bertolotti et al., 2017, Watanabe et al., 2013), and indication (Wu et al., 2013, Johansen et al., 2014). Other research found non-significant associations between statin use and marital status (Selmer et al., 2009). Survey weights supplied by TILDA were applied to reduce non-response bias. The derivation of these weights is described in Appendix 4. The characteristics used for calibration were age, sex and education, sourced from the Quarterly National Household Survey 2010 compiled by the Irish Central Statistics Office (Whelan and Savva, 2013). Maximum missing data was < 1%.

The SCORE tool was used to assess 10-year risk of a fatal CVD event in participants without established CVD or diabetes aged 50-64 years, stratified as either above or below a 5% risk threshold (Conroy et al., 2003). A multivariable logistic regression model was also used to examine how statin utilisation related to SCORE risk, controlling for cardiovascular indication, healthcare utilisation and socio-demographic factors.

The statistical software Stata /MP V 13.1 was used to conduct the analyses.

### 3.4 Results

The characteristics of the sample are described in Table 3-1.

Table 3-1: Sample Descriptive Statistics

Variable	Categories	All (%)	Female (%)	Male (%)
Statins	Yes	30.2	28.8	32.4
	No	69.8	71.1	67.5
Age	50-64 years	60.3	61.9	58.3
	65-74 years	26.5	24.8	28.5
	75+ years	13.2	13.2	12.2
Sex	Female	53.6	N/A	N/A
	Male	46.4	N/A	N/A
Education	Primary/none	25.6	23.3	28.2
	Secondary	41.3	42.2	40.0
	Third level/higher	33.1	34.4	31.6

Income (per annum)	<€10,000	9.8	10.5	9.0
	≥ €10,000, <€20,000	18.7	19.8	17.4
	≥ €20,000, <€40,000	34.2	34.0	34.3
	≥ €40,000, <€70,000	20.3	18.0	24.0
	≥ €70,000, <€2,000,000	8.8	8.0	9.7
	Missing	8.2	10.5	5.6
Social class	Professional, managerial and technical workers	24.9	22.9	27.1
	Non-manual and skilled manual workers	21.0	21.7	20.0
	Semi-skilled and unskilled workers	11.6	10.3	13.2
	Farmers	5.7	1.6	10.3
	Not applicable	26.3	37.6	13.1
	Unknown and refused	10.6	5.7	16.1
Insurance	No cover	10.4	9.2	11.7
	Medical insurance	43.6	45.1	47.0
	Medical card	46.0	45.7	41.2
GP visits	0 visits	12.6	11.2	13.7
	1-2 visits	36.9	35.7	38.2
	3-4 visits	26.6	27.3	25.8
	5-6 visits	11.5	12.6	10.3
	7+ visits	12.4	13.2	11.9
Polypharmacy	No	80.0	79.3	79.8
	Yes	20.0	20.2	19.5
Lives with	Living alone	21.4	23.7	19.8
	Living with spouse/partner	38.8	36.1	42.0
	Living with others	39.8	41.0	38.1
Location	Dublin city or town	26.3	26.9	25.5
	Another town or city	27.3	27.0	27.4
	Rural area	46.5	45.9	46.9
Indication	Myocardial infarction (MI)	4.5	2.3	7.3
	Ischaemic heart disease (IHD)	3.2	2.8	4.0
	Stroke	2.7	3.0	2.7

Potential atherosclerotic conditions (PAC)	8.7	10.6	7.9
Diabetes	5.0	4.6	5.9
Hypertension	23.0	28.0	21.2
High cholesterol	17.0	21.1	15.0
No CVD related diagnosis	36.0	42.2	34.9

Source: Analysis of The Irish Longitudinal Study on Ageing (TILDA) Wave 1 data.

### 3.4.1 Prevalence According to Age and Gender

Table 3-2 shows descriptive analyses for prevalence by indication and age. Within this sample of 5,618 people, 30.5% were currently taking statins. Appendices 5 and 6 show corresponding data for females and males respectively, showing that higher proportions of men (32.5%) than women (28.8%) take statins (the 95% CIs for these groups do not overlap). Table 3-2 also shows the prevalence of statin use in each age category for the sample. Statin utilisation increased monotonically with age; 22.6% of those aged 50 to 64 years, 41.1% of those aged 65 to 74 years, and 45.6% for those aged 75 years or more. The increased use of statins with increasing age was observed in each gender category (Appendices 5 and 6), with lower proportions of women than men taking statins in each age category.

### 3.4.2 Prevalence According to Indication

Table 3-2 shows, for example, that of the 250 people who have had MI, 185 are taking statins. This means that 74% of those who have had MI take statins. As the proportion of people who have had MI is low in the population, this represents 10.9% of statin users. On the other hand, a smaller proportion of those with ‘high cholesterol’ take statins (44.1%), but as they represent a larger proportion of the population, this accounts for 24.5% of all statin users. The results clearly show high, though not universal, uptake rates of statins for those with established CVD (e.g. 74.0% for MI and 73.7% for IHD), with lower, but still highly significant uptake rates for primary prevention (e.g. 34.8% for hypertension and 44.1% for high cholesterol).

Those with established CVD (i.e. MI, IHD, Stroke and PAC) accounted for 34.9% of those taking statins, while those with diabetes accounted for 9.4% (Table 3-2). Therefore, overall, those without established CVD or diabetes accounted for 55.7% of those taking

statins. However, of all women taking statins, 64.7% did not have CVD or diabetes compared to 46.2% of men (Appendices 5 and 6). Overall, 65.0% of statin-users did not have a prior history of established CVD and were taking statins for primary prevention. The proportion of men taking statins without a history of CVD was 57.3%, while the corresponding proportion for women was 72.7%. These high proportions reflect, in part, the greater proportions of the cohort with no history of CVD.

Table 3-2: Statin Utilisation According to Age and Indication Among TILDA Participants (Wave 1) Aged over 50 Years

	Age	Number	Number on statins	% taking statins [95% CI]	MI	IHD	Stroke	PAC	Diabetes	Hyper-tension	High cholesterol	No diagnosis
	50-64	3,387	765	22.6% [21.2%-24.0%]	56	29	25	73	71	227	251	29
	65-74	1,488	611	41.1% [38.6%-43.6%]	72	56	39	60	61	147	136	34
	75+	743	339	45.6% [42.1%-49.2%]	57	47	28	51	28	73	30	19
	Total	5,618	1,715	30.5% [29.3%-31.7%]	185	132	92	184	160	447	417	82
Total with diagnosis whether on statins or not					250	179	150	484	277	1,284	945	2,007
% of those with indication on statins [95% CI]					74.0% [68.2%-79.1%]	73.7% [66.7%-79.7%]	61.3% [53.2%-68.9%]	38.0% [33.8%-42.4%]	57.8% [51.8%-63.5%]	34.8% [32.3%-37.5%]	44.1% [41.0%-47.3%]	4.1% [3.3%-5.0%]
% of those on statins with indication					10.9%	7.8%	5.4%	10.8%	9.4%	26.3%	24.5%	4.8%

Source: Analysis of The Irish Longitudinal Study on Ageing (TILDA) Wave 1 data.

Notes: The column ‘Number’ represents the total number of individuals in the TILDA dataset by age group and overall, whether they are taking a statin or not, while the column ‘Number on statins’ represents the total number of individuals taking a statin. The column ‘% taking statins’ is the number on statins as a percentage of all individuals by age group and overall. The subsequent eight columns present the numbers or percentages on statins for each of the indication categories. MI= myocardial infarction; IHD = Ischaemic Heart Disease; PAC= potential atherosclerotic conditions.

### 3.4.3 Factors Associated with Statin Utilisation

Table 3-3 presents the estimated odds ratios obtained for each variable included in the final multivariable logistic regression model, adjusting for all other variables in the model.

Overall those aged 65 to 74 years were more likely to be prescribed a statin than those aged 50 to 64 years (OR 1.38; CI 1.16-1.65), as were those in the oldest age bracket, 75 and over (OR 1.33; CI 1.04-1.69).

The number of times a person reported visiting a GP in the previous year was predictive of the likelihood of taking a statin relative to those who had not reported visiting a GP in the previous year (Table 3-3). Polypharmacy, defined as taking five or more medications, was also strongly predictive of statin utilisation (OR 1.74; CI 1.39-2.19). People who were living with a spouse or partner were more likely than those living alone to be taking a statin (OR 1.35; CI 1.10 to 1.65). The odds of taking statins for those with a diagnosis of MI was, as expected, relatively high compared to those without MI. All indications were statistically significant except for the IHD category.

Table 3-3: Adjusted Odds Ratios of Statin Use from Multivariable Logistic Regression Model

		<b>OR</b>	<b>p-value</b>	<b>95% CI</b>
Age	50-64 (Base)	1.00	-	-
	65-74	1.38	<0.000	1.16-1.65
	75+	1.33	0.022	1.04-1.69
GPvisits	0 (Base)	1.00	-	-
	1-2 visits	2.46	<0.000	1.80-3.35
	3-4 visits	3.24	<0.000	2.34-4.47
	5-6 visits	2.98	<0.000	2.08-4.26
	7+ visits	2.51	<0.000	1.73-3.63
Polypharmacy	No	1.00	-	-
	Yes	1.74	<0.000	1.39-2.19
Lives with	Lives alone (Base)	1.00	-	-
	Lives with spouse/partner	1.35	0.004	1.10-1.65
	Lives with other	0.95	0.640	0.76-1.18
Indication	MI (Base)	1.00	-	-

	IHD	0.98	0.948	0.59-1.64
	Stroke	0.51	0.009	0.31-0.84
	PAC	0.25	<0.000	0.17-0.36
	Diabetes	0.50	0.002	0.33-0.77
	Hypertension	0.21	<0.000	0.15-0.31
	High cholesterol	0.44	<0.000	0.31-0.64
	None of above	0.03	<0.000	0.02-0.04
Observations	5,528			
Pseudo-R <sup>2</sup>	0.2474			

Source: Analysis of The Irish Longitudinal Study on Ageing (TILDA) Wave 1 data.

Note: The model is a stepwise (backward selection) multivariable binary logistic model, applying a 10% significance level for removal. This means that only variables found to be statistically significant at the 10% level are included in the final model. MI = myocardial infarction; IHD = Ischaemic Heart Disease; PAC = potential atherosclerotic conditions.

The odds ratios for socio-economic variables such as income, social class and education level were not found to be statistically significant, nor were odds ratios for gender, health insurance status or whether the person lived in a rural or urban area.

#### **3.4.4 SCORE Analysis**

SCORE risk was calculated in those without CVD or diabetes whose LDL and/or TC levels were above the recommended thresholds (n=3,551). 18% of those whose SCORE result was  $\geq 5\%$  were taking statins. 17% of those with a SCORE of  $<5\%$  were taking statins (results not shown). However, it was not possible to interpret whether their SCORE risk level had been altered by statin utilisation. Nor could I ascertain what proportion in either risk group had potentially discontinued statins previously utilised.

In a separate multivariable model using the subsample of those without CVD or diabetes whose LDL and/or TC levels were above the recommended thresholds, SCORE risk category was not found to be statistically significantly related to taking a statin (results not presented).

## 3.5 Discussion

### 3.5.1 Key Results

I found that almost one third of adults over 50 in this Irish cohort were taking statins. Almost two thirds of these took statins for the primary prevention of CVD, but there was a notable difference between men and women. Almost three quarters of women taking statins were doing so for primary prevention, compared to just over half of men. Prevalence of statin utilisation was found to increase with age.

Diagnostic indication was a predictor for increased likelihood of taking statins, with those with a history of MI, as expected, having the highest prevalence of statin utilisation. However, although the indication hierarchy used implied an ordering of indications corresponding to priorities for statin treatment, the likelihood of utilising a statin did not uniformly follow this order. Both the diagnoses 'Diabetes' and 'High Cholesterol' were found to have higher odds than warranted according to the hierarchy. However, it should be noted that this may be due to the numbers being small in some indication categories, leading to wide confidence intervals, and thus the disparity in ordering should not be over-interpreted. Polypharmacy, frequency of GP visits and living arrangements were also significantly associated with the likelihood of taking a statin, while controlling for all other variables in the model.

The 2007 European Society of Cardiology clinical guidelines recommended that those with a SCORE of over 5% be considered for statin treatment (Graham et al., 2007, Norris et al., 2014). This study found that less than a quarter of those above this threshold were utilising statins, as were one fifth of those below. This may indicate that GPs or some other doctors initiating statin therapy do not use SCORE to risk assess their patients, but due to the limitations of the data it is difficult to interpret if this is the case. A recent UK study of a primary care database found that most patients initiated on statins did not have a risk score recorded. While statins were initiated in 27.5% of clinical encounters and a risk score was recorded in 80% of all encounters, only 7.5% of encounters recorded both a risk score and subsequent statin initiation (Finnikin et al., 2017).

### **3.5.2 Strengths and Limitations**

A strength of this analysis was that it was conducted on a large, nationally representative sample of community-dwelling adults, aged over 50 in Ireland. Recording medication use directly from respondents with verification allows a closer examination of real life usage compared to dispensing data that may not account for some elements of non-adherence. Survey weights were applied in the multivariable analysis to reduce potential bias from non-response in the TILDA data collection. This means that my findings are therefore more likely to be representative. These factors will allow for the generalisation of my findings to community living adults aged 50 and over in Ireland. This study will therefore be useful for cross-country comparisons of statin utilisation, as well as the patterns by which these drugs are prescribed. The breakdown of utilisation according to indication will inform the debate on the appropriateness of statin prescribing in subgroups of gender and age, diagnostic indications and those who fall into the primary and secondary prevention categories.

The study is limited in that it relies on self-reported doctor diagnoses and recall of the number of GP visits, which may be subject to recall bias. When constructing the indication hierarchy, the reported diagnosis of 'Any Other Heart Trouble' could not be used and so I may have underestimated the prevalence of those within the secondary prevention category. The diagnostic category 'Potential Atherosclerotic Conditions' may include diagnoses that are not atherosclerotic in origin. Also, the diagnostic category 'Peripheral Arterial Disease' could not be ascertained due to limitations of the data gathered in TILDA. I had no information on those who have declined or discontinued statins and it is known that poor adherence to statins is common (Norris et al., 2014). I could not distinguish those with type I and type II diabetes. This is relevant as the 2007 guidelines distinguish between these groups (Graham et al., 2007). However, numbers of people with type 1 diabetes are relatively small compared to those with type 2 in the over 50 age group. Although diagnosis of familial hypercholesterolaemia was not clear in the data, I removed those whose LDL levels were  $>6\text{mmol/L}$  from the sample. As this comprised 16 people this would not have affected results. Finally, it should be noted that given the cross-sectional nature of the data and the possibility of residual confounding, the results from the multivariable analysis should be considered as statistical associations rather than causal effects.

### **3.5.3 Interpretation**

#### *Primary and Secondary Prevention*

While there is higher prescribing of statins for those with established CVD as would be expected, my finding that a large proportion of statins are used for the primary prevention of CVD is in line with international findings that the distribution of statin prescribing has shifted towards those at the lower end of the indication hierarchy (Wallach Kildemoes et al., 2008, Feely and Bennett, 2008).

Previous Irish research, using a subsample of TILDA data (50-64 year olds), found that despite clinical guidelines recommending the use of statins in those with CVD or diabetes, treatment prevalence was considered low in these groups, at 69% and 57% respectively (Murphy et al., 2015). In addition, this previous study found a low level of treatment prevalence in those without CVD and diabetes, but whose SCORE was  $\geq 5\%$ . Both findings are in line with the current study. However, by stratifying participants into the indication hierarchy, this study allowed those in the ‘primary prevention’ group to be analysed in greater detail.

Overall, 28.8% of women and 32.5% of men in the cohort were taking statins. I found that the majority (65.0%) of the cohort was utilising statins for primary prevention of CVD, with a notable difference between men (57.3%) and women (72.7%).

#### *Age*

This study showed that the odds of statin usage were higher at older age groups compared to the 50-64 year old base category. This was similar to findings in Denmark (Wallach Kildemoes et al., 2012b), New Zealand (Norris et al., 2014) and the UK (Wu et al., 2013, Johansen et al., 2014) except that a decrease in utilisation was found in these studies in the oldest age groups.

#### *Socioeconomic Factors*

In line with a previous Irish study (Murphy et al., 2015), I did not find education level, social class, income or whether the person had medical insurance or a medical card to be statistically significant predictors of statin usage. An exception was found in the previous

study for those at high SCORE risk, who were twice as likely to be taking statins if eligible for a medical card.

Conflicting findings about statin utilisation and socio-economic factors have been reported in studies from other countries (Kitzmilller et al., 2013, Condliffe et al., 2010, Selmer et al., 2009, DeWilde et al., 2003, Norris et al., 2014, Wu et al., 2013). These differences may be a result of differences in access and entitlements within health systems, as well as differing social, political and cultural contexts (Walley et al., 2004). Countries may vary in reimbursement regulation (Walley et al., 2005, Selmer et al., 2009, Norris et al., 2014), type of insurance cover (such as Medicaid, Medicare and private insurance in the US) (Condliffe et al., 2010), clinical guideline recommendations (Johansen et al., 2014), local medical and patient culture, as well as differences in demand from patients in differing socio-economic groups (Walley et al., 2005, Norris et al., 2014).

#### *Number of GP Visits*

Controlling for indication, a person was more likely to be using a statin if they had visited their GP in the previous year than if they had not. The estimated OR increased with number of GP visits until 3-4 visits and decreased thereafter, though there was considerable overlap in the 95% CIs for different frequencies of GP visits. In their study of factors influencing the prescribing of statins in the UK, Wu et al. (2013) found that statin prescribing increased with number of blood pressure measurements, a proxy for GP visits and perception of CVD risk. However, the highest number of GP visits described was 4 or more and their study may have shown a similar pattern to ours were the number of visits stratified in a similar manner.

#### *Polypharmacy*

Polypharmacy, commonly defined as the use of five or more regular medicines, was found to be a strong predictor of statin prescription. In other words, controlling for clinical indication, a person receiving five or more medicines (excluding statins) was more likely to be taking a statin. A recent Irish study found that the prevalence of polypharmacy in those over 65 years in 2012 was 60% (Moriarty et al., 2015), and that statins were the drug category prescribed to the highest number of individuals. Another

study reported that lipid-modifying drugs were the most commonly reported medication class (69%), along with anti-thrombolytics, used by those reporting polypharmacy (Richardson et al., 2012). This finding raises questions as to why, controlling for diagnostic indication, someone receiving five or more medicines would be more likely to receive a statin. This could be based on differences in patient preferences as well as challenges to following clinical guidelines for patients with multimorbidity, which is closely linked with polypharmacy (Wallace et al., 2015). Some studies have found an association between polypharmacy and increased likelihood of statin use (Bertolotti et al., 2017, Watanabe et al., 2013) and adherence to statins (Wawruch et al., 2017, Grant et al., 2004), while others found that people subject to polypharmacy were less likely to adhere to medicines, including statins (Mohammed et al., 2016). Further qualitative research is recommended to explore this finding.

#### *Indication Hierarchy*

The indication hierarchy implied an ordering of indications (Wallach Kildemoes et al., 2012a) corresponding to priorities described in European guidelines (Graham et al., 2007). However, the analysis showed that the likelihood of utilising a statin did not exactly follow this order of prescribing priority. Both ‘High Cholesterol’ and ‘Diabetes’ were found to have higher odds than warranted according to the hierarchy, though again I acknowledge the caveat that this may be due to small numbers for some indication categories. Those with high cholesterol were more likely to receive statins than those with PAC and hypertension, whereas those with SCOREs over the recommended risk threshold had low levels of statin utilisation. This could imply an over-emphasis on high cholesterol, a single risk factor, as a reason to prescribe rather than prescribing based on overall risk assessment. This finding corresponds with those from the US (Johansen et al., 2014), Norway (Selmer et al., 2009), the UK (Wu et al., 2013) and Australia (Schilling et al., 2016).

In my study, 57.8% of people with diabetes were taking statins and they accounted for 9.4% of prevalent statin users. This finding was similar to previous Irish (Murphy et al., 2015) and Danish findings (Wallach Kildemoes et al., 2015). Two US studies found that 48% (Wu et al., 2013) of ‘eligible diabetics’ and 52% (Johansen et al., 2014) of people

with both diabetes and hyperlipidaemia were taking statins. In those without a diagnosis of hyperlipidaemia, this fell to 12%.

### **3.6 Conclusion**

This study describes statin utilisation in a representative sample of over 50s in Ireland. I show high, though not universal, uptake rates of statins for those with established CVD, with lower, but still highly significant uptake rates for primary prevention. Given the on-going debate on the appropriateness of statin use in primary prevention (Wallach Kildemoes et al., 2015, Godlee, 2014b, Fairman and Curtiss, 2011), it is significant that such a large proportion of Irish users fall into this category, particularly women. In addition, the possible focus on hyperlipidaemia as a reason for prescribing instead of overall CVD risk may indicate an overemphasis on this single risk factor (Johansen et al., 2014, Schilling et al., 2016). Polypharmacy, controlling for indication, was strongly associated with statin use. This finding warrants further investigation.

Statin use is widely prescribed and command a large share of drug expenditure in Ireland and other countries. An increasingly larger proportion of the population are using statins, and this is becoming very resource intensive and arguably unsustainable. The evidence base for statin use in various diagnostic categories varies (Chang et al., 2013, Wallach Kildemoes et al., 2015) and thus, the benefit-to-risk ratios for each also vary. There have been concerns about the medicalisation of risk factors such as mild hypercholesterolaemia (Gotzsche, 2002). Various commentators have pointed out that the benefits of prescribing a medicine must outweigh the harms (Fineberg, 2012) and that the budget impact of thresholds for treatment needs to be considered (Epstein et al., 2016). However, uncertainties abound when deciding upon cost-effective treatment thresholds (Macdonald and Loder, 2015, Busfield, 2015). It would therefore seem appropriate to consider whether widespread use of statins in some of these diagnostic categories represents the best use of scarce resources, particularly in low risk groups (Taylor et al., 2013).

The debate on the appropriate use of statins for primary prevention of CVD is on-going and highly topical (Godlee, 2014b, Godlee, 2016, Goldacre and Smeeth, 2014, Hawkes, 2014, Hawkes, 2015, Wise, 2015). At the heart of this debate is the question as to whether

the benefits of taking statins outweigh the harms and costs for patients in the primary prevention category. The first step towards answering this question is to consider current utilisation and indication for use, as I have done, which provide important contextual information for the debate on statin use.

# 4 Statins for the Primary Prevention of Cardiovascular Disease: An Overview of Systematic Reviews

## 4.1 Introduction

As noted, the last thirty years have seen a large increase in the utilisation of statins (Walley et al., 2005, Feely et al., 2000, Wallach Kildemoes et al., 2008, DeWilde et al., 2003), which is consistent with changes in recommendations in clinical guidelines. (Moynihan et al., 2013). The analysis presented in Chapter 3 found that almost two thirds of people who were taking statins did so for primary prevention (Byrne et al., 2018), thus it is important to establish the evidence upon which statins for primary prevention is based.

Several systematic reviews (SRs) investigating the use of statins for the primary prevention of CVD have been published reaching varying conclusions (Ray et al., 2010, de Lorgeril and Rabaeus, 2016, Ijioma and Robinson, 2015, Petretta et al., 2010, Brugts et al., 2009, de Vries et al., 2012). However, most published SRs reported on trials that included a proportion of participants with a history of CVD (Taylor et al., 2013, Chou et al., 2016, Thavendiranathan et al., 2006). In addition, the primary prevention population is heterogeneous, ranging from those at very low risk of CVD to those considered ‘risk equivalent’ to those in the secondary prevention category. The latter, for example, includes people with diabetes mellitus (DM) exhibiting target organ damage, or people with chronic kidney disease (Catapano et al., 2016). The net benefit or absolute risk reduction achieved with statin therapy is critically dependent on the baseline risk. Therefore, the outcomes reported in the SRs that are stratified by baseline risk or by gender are of particular interest, since these data are the most pertinent to clinical decision making with individual patients.

To address this evidence gap and support decision making, I undertook an overview of SRs that reported on *exclusively* primary prevention trials or individual patient data (IPD) of trial participants using only data from patients without established CVD.

## 4.2 Methods

This overview was conducted according to the methods of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011). The protocol for the overview was published on PROSPERO (Byrne et al., 2017). I included any SR of RCTs or IPD from RCTs, in any language, which examined the effectiveness of statins versus placebo or no treatment exclusively in those without prior CVD. I searched for the following outcomes: 1. all-cause mortality; 2. fatal and non-fatal coronary heart disease (CHD), CVD events including stroke; 3. composite endpoints; 4. any of these outcomes stratified by a calculation of future risk of CVD or by gender (see Box 4.1).

Box 4.1: PICOTSS (Patients, Interventions, Comparators, Outcomes, Timing, Setting and Study Design) Format

### **Patients**

- Adults  $\geq 18$  years of age
- Without established CVD

### **Interventions**

- Statins (HMG-CoA reductase inhibitors)

### **Comparators**

- Placebo
- Control

### **Outcomes**

- All-cause mortality
- Fatal and non-fatal CHD, CVD and stroke events
- Combined endpoint (fatal and non-fatal CHD, CHD and stroke events)
- Any of the above outcomes stratified by a calculation of future risk of CVD or by gender

### **Timing**

- Studies of any duration

The search strategy, terms and databases were chosen with the assistance of a health sciences librarian and are described in Appendices 7 and 8. I searched the Cochrane Database of Systematic Reviews, MEDLINE, Embase, PubMed, Scopus and PROSPERO from the date of the first statin's approval in 1987 (Endo, 2004) to June, 2017.

Two overview authors (Paula Byrne (PB) and Amelia Smith (AS)) independently screened search results by title and abstract and obtained full text versions of the articles identified by both as potentially relevant. PB and AS selected relevant articles by reading the full texts and applying the inclusion and exclusion criteria. PB and AS used Covidence systematic review software to manage the searches and extraction of data (Covidence systematic review software). Any differences of opinion on inclusion were resolved by consulting another overview author (Susan Smith (SS) or John Cullinan (JC)).

#### **4.2.1 Data Collection and Analysis**

PB performed data extraction, while AS independently checked the extracted data. SRs were extracted that fulfilled inclusion criteria, that is, SRs of RCTs or IPD from RCTs, in any language, which examined the effectiveness of statins versus placebo or no treatment exclusively in those without prior CVD. We extracted data on outcomes of relevance; all-cause mortality; CHD, CVD and stroke events; composite endpoints; any of these outcomes stratified by a calculation of future risk of CVD or by gender. Both reviewers independently assessed the methodological quality of the included reviews using the R-AMSTAR tool (Kung et al., 2010). One of the included SRs, published by the Cholesterol Treatment Trialists Collaboration (CTT), consisted of analyses of IPD and was reported in two publications based on the same trials, one reporting results overall (Mihaylova et al., 2012) and one that included analyses stratified by gender (Fulcher et al., 2015). Some of the methods were described not in the SR itself but in other referenced CTT papers and in the CTT protocol, which was published in 1995 (Baigent et al., 2005, Baigent et al., 2010, Downs et al., 1995). As we found some limitations in using R-AMSTAR in the context of IPD, we further assessed CTT, and the secondary papers describing their methodology, using the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data (PRISMA-IPD)

checklist (Stewart et al., 2015). We searched the SRs for any assessments of the quality of evidence of included trials such as GRADE, Cochrane Risk of Bias or the Jadad Scale. I undertook a narrative synthesis of the included reviews and summarised their main results on the effectiveness of statins regarding the outcomes of relevance and those outcomes stratified by baseline risk and gender.

## **4.3 Results**

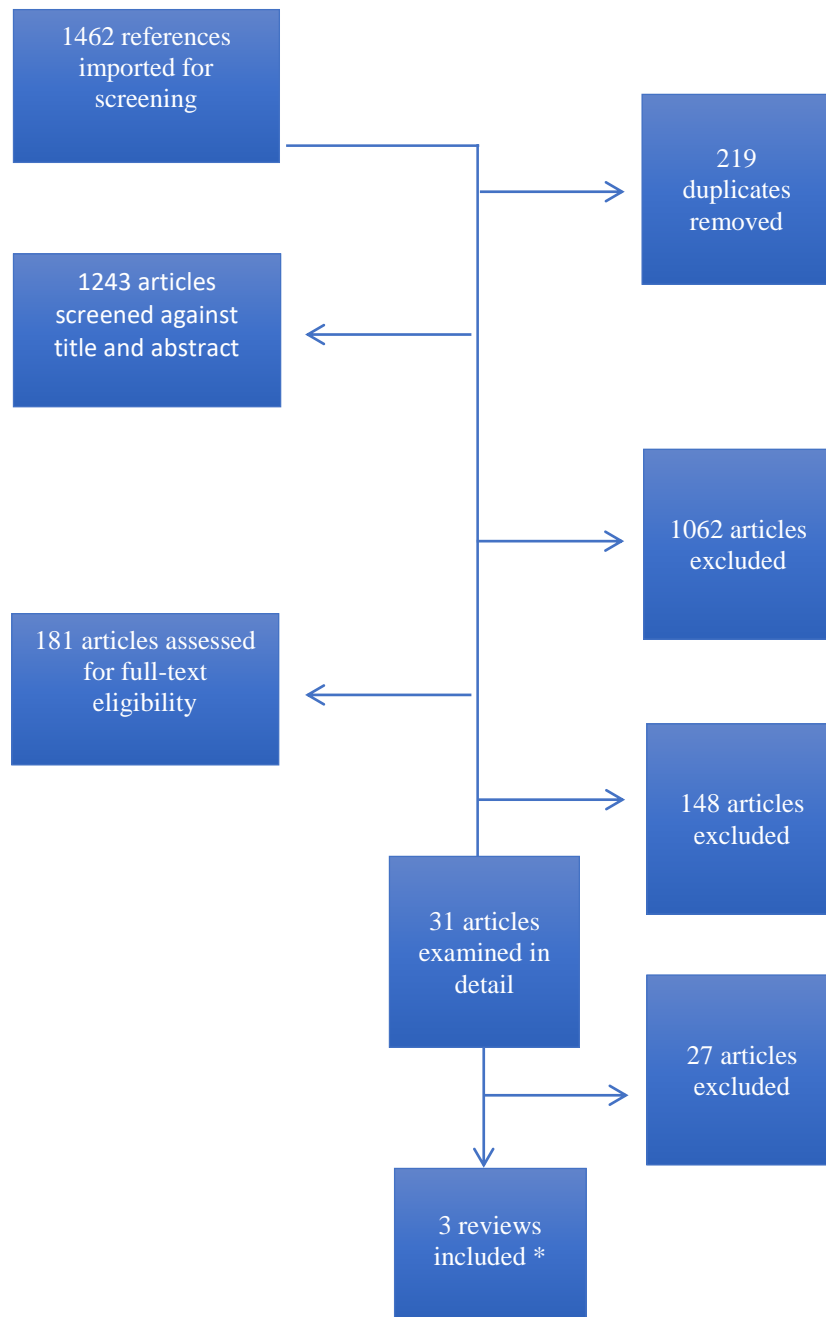
### **4.3.1 Search Results**

My initial searches yielded 1,462 results of which 181 were evaluated as full text articles following title and abstract screening. 31 full text articles were analysed in detail. I supplemented the electronic search by scanning the reference lists of the full text articles we read. No further SRs were identified. Reasons for exclusion and references to 27 final excluded articles are presented in Appendix 9. On the basis of the search and extraction strategy, three SRs were included in this overview. One of the included SRs was reported in two separate publications but included the same trial data, so was treated as a single systematic review for the purpose of this overview (see Figure 4.1). Many excluded SRs did not specify the proportion of participants without CVD that had been included. Some primary prevention SRs included trials with up to 50% of participants with CVD, (Mills et al., 2008) while the most up to date Cochrane review included trials with up to 10% of participants having CVD (Taylor et al., 2013).

### **4.3.2 Characteristics of Included Studies**

Of the three included SRs, two comprised analyses of aggregate data from RCTs (Ray et al., 2010, Mora et al., 2010) and one, (Mihaylova et al., 2012, Fulcher et al., 2015), presented analyses of IPD from the CTT. Table 4-1 describes the characteristics of the included reviews, while Table 4-2 describes the population demographics reported in each SR.

Figure 4.1: Flowchart of Included Systematic Reviews



Note: \* One of these included reviews comprised two publications arising from the CTT analyses of IPD from the same trials.

Table 4-1: Characteristics of the Included Systematic Reviews

Review (year)	Population	Intervention	Comparator	Included studies			Quality of included reviews	Total participants	Baseline risk of participants	Outcomes reported	Sub-group analysis of outcomes	Synthesis	Last search date
				RCTs (n)	Mean follow-up duration (years)	Quality of evidence of included trials GRADE							
CTT 2012 and 2015	Men and women without prevalent CVD at baseline	Statin	Control	22	4.8	NR	27	134,537	<5%; ≥5% to <10%; ≥10% to <20%; ≥20% to <30%; ≥30%	Any deaths Any vascular death Non-vascular death Major coronary events Major vascular events	All outcomes by baseline risk profile Major vascular events by gender	IPD meta-analysis	2011
Mora 2010	Women without prevalent CVD at baseline	Statin	Control	3	>1	NR	19	13,154	N/A		Total CVD in women Total mortality in women	RCT meta-analysis	2009
Ray 2010	Men and women without prevalent CVD at baseline	Statin	Control	11	3.7	NR	32	65,229	N/A	All-cause mortality		RCT meta-analysis	2009

Table 4-2: Population Demographics

Review	Participants (n)	Gender	% Male	Mean age	With diabetes %	Smokers %	Mean SBP Mm HG	LDL-C mmol/L*
CTT 2012 and 2015	134,537	Women and men	59**	65.3 (women) 62.0 (men)	24.5 (women) 19.4 (men)	15.4 (women) 9.4 (men)	141.2 (women) 139.3 (men)	3.6 (women) 3.6 (men)
Mora et al. 2010	13,154	Women	0	64***	7***	NR	NR	NR
Ray et al. 2010	65,229	Women and men	65	62	19	23	141	3.6

Notes: SBP =systolic blood pressure; LDL-C =low-density lipoprotein cholesterol; NR =not reported.

\* SI conversion factor – to convert LDL-C to mg/dL divide by 0.0259.

\*\* This proportion was calculated from Table 2 in: Fulcher J, O’Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Cholesterol Treatment Trialists’(CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397-405.

\*\*\* This proportion was calculated from Figure 2 in: Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia results from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation*. 2010;121(9):1069-77.

The CTT analyses included IPD from 22 trials of statin versus control as well as five of more versus less statin. However, the trials of more versus less statins did not include any primary prevention participants, therefore I assume, although it is not stated in the SR, that all analyses in those with ‘no known history of vascular disease’ are taken from only the statin versus control trials and I included only these analyses in the overview as per the protocol. Appendix 10 describes analyses from the included SRs that were not included in this overview.

Ray et al. (2010) included 11 trials with additional unpublished data from authors that provided data on primary prevention participants. Mora et al. (2010) included three exclusively primary prevention trials in women only. Two types of data therefore are included in the overview, IPD and aggregate data from trials.

The overlap of included reviews is reported in Table 4-3 (overleaf). While all SRs included overlapping RCTs, IPD were used by CTT, Ray et al. reported previously unpublished data and outcomes were reported differently across the three included systematic reviews.

### **4.3.3 Outcomes Reported**

All three SRs reported outcomes for all-cause mortality, one of which, Mora et al., was in women only. CTT reported outcomes for vascular deaths, non-vascular deaths, major coronary events (defined as non-fatal myocardial infarction or coronary death) and major vascular events (defined as major coronary events, coronary revascularisation and stroke).

In addition, all outcomes reported by CTT were stratified by the participants’ five-year vascular risk at baseline. The risk categories reported in CTT describe a person’s estimated five-year risk of having a major vascular event and were stratified as follows; <5%; ≥5% to <10%; ≥10% to <20%; ≥20% to <30%; and ≥30%. This method of calculating risk was modelled by CTT and how these categories relate to more commonly used methods such as SCORE, QRISK and Framingham is unclear. However, Robinson et al. (2016) estimated CTT’s ≥5% to <10% five-year vascular risk to be nearly identical to the more standard US 10-yr ASCVD event rate. The outcome major vascular events

was also stratified by gender by CTT and Mora et al. reported results for the composite outcome total CVD events in women. (See Appendix 10 for outcomes that were reported in the included SRs but which I did not include in this overview.)

Table 4-3: Trial Overlap of Included Systematic Reviews

Included Trials	CTT	Mora	Ray
AFCAPS/TexCAPS	✓	✓	✓*
ALERT	✓		
ALLHAT-LLT	✓		✓**
ALLIANCE	✓		
ASCOT-LLA	✓		✓**
ASPEN	✓		✓**
AURORA	✓		
CARDS	✓		✓
CARE	✓		
CORONA	✓		
4D	✓		
GISSI-HF	✓		
GISSI-P	✓		
HPS	✓		
HYRIM			✓*
JUPITER	✓	✓	✓
LIPID	✓		
LIPS	✓		
MEGA	✓	✓	✓
Post-CABG	✓		
PREVEND-IT			✓**
PROSPER	✓		✓**
4S	✓		
WOSCOPS	✓		✓

Notes: \* Provided hitherto unpublished tabular data on all-cause mortality. \*\* Shared tabular data on subset of participants without CVD.

#### 4.3.4 Quality Assessment of Included Reviews

##### 1. R-AMSTAR:

The CTT SR received a R-AMSTAR score of 27. The reviews by Mora et al. and Ray et al. were assigned ratings of 19 and 32 respectively, out of a maximum score of 44 (See Table 4-4).

Table 4-4: R-AMSTAR Assessment per Systematic Review

<b>Review</b>	<b>R-AMSTAR criteria</b>											
	Was an ‘‘a priori’’ design provided? The research question and inclusion criteria should be established before the conduct of the review?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Were the methods used to combine the findings of studies appropriate?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest included?	
	<b>R-AMSTAR score per review</b>											<b>Total</b>
<b>CTT</b>	4	1	2	2	2	4	2	2	4	1	3	27
<b>Mora et al.</b>	3	1	1	2	1	1	2	2	3	1	2	19
<b>Ray et al.</b>	3	4	3	1	2	3	3	4	3	4	2	32

In general, the included SRs scored lowest in criteria describing search strategies, excluded studies and reasons for exclusion. Neither Mora et al. nor CTT clearly reported their search strategy, methods of study selection or extraction or provided lists and characteristics of excluded studies; nor how disagreements among extractors were resolved or if two independent researchers extracted data from the included studies. Across the included SRs, the highest scoring criterion was for the statistical methods of combining included studies.

## 2. PRISMA-IPD:

Using PRISMA-IPD as well as R-AMSTAR, I was still unable to assess potential risk of bias in the CTT SR including how IPD were collected, requested and managed, whether IPD were sought and not available from other trials, the full electronic search strategy, details of databases searched, methods for resolving disagreements between those extracting studies, lists and characteristics of excluded studies, assessment of risk of bias in included RCTs, and assessment of publication bias. It should be noted that this checklist was published in 2015, which is after the publication of CTT's SR. However, it would seem reasonable to expect that all items included in the PRISMA-IPD checklist would be incorporated in IPD analysis. The CTT protocol notes that publication bias can be avoided by 'prospectively planning an overview based on individual patient data from all relevant randomized trials'. However, no tests for publication bias were reported. Ray et al. was the only included SR that reported on publication bias and assessed this using a funnel plot and Egger's test and found no strong evidence of publication bias ( $p=.50$ ).

### **4.3.5 Risk of Bias from the Primary Randomised Control Trials**

None of the SRs reported on the risk of bias in their included primary trials using GRADE, Cochrane Risk of Bias or the Jadad Scale.

### **4.3.6 Effectiveness of Statins**

Due to the variability in the reviews and different outcomes reported, I have not attempted to combine or re-meta-analyse results and have presented a narrative synthesis as an overview of all results. I found a trend towards reduced all-cause mortality in the three systematic reviews, though only one of the three showed a statistically significant difference. CTT reported statistically significant relative risk (RR) reductions in 'any

deaths' (RR 0.91 (CI 0.85 to 0.97)). Ray et al. conducted both fixed and random effects meta-analyses, with and without two trials reporting results for people with diabetes. There were no significant reductions in all-cause mortality in any of the meta-analyses; random effects models RR 0.91 (CI 0.83 to 1.01) including diabetes trials; fixed effects models RR 0.93 (CI 0.86 to 1.00) including diabetes trials; random effects models RR 0.92 (CI 0.84 to 1.02) excluding diabetes trials; fixed effects models RR 0.94 (CI 0.86 to 1.01) excluding diabetes trials. Mora et al. found no significant reduction in total mortality (RR 0.78 (CI 0.53 to 1.15)) in women.

CTT reported significant reductions in any vascular death (RR 0.85 (CI 0.77 to 0.95)) and non-significant reductions in non-vascular death (RR 0.97 (CI 0.88 to 1.07)).

In addition, CTT reported results stratified by baseline risk category. There were non-significant reductions reported by CTT in 'any deaths' except at one level of risk. Non-significant results for vascular deaths were reported in all risk categories. Three risk categories were found to have non-significant increases in non-vascular deaths, while two had non-significant reductions in the outcome. There were reductions reported in all risk categories for major coronary events and major vascular events, when stratified by baseline risk category but these were not statistically significant in the two highest risk categories – see Table 4-5.

Table 4-5: Reported Results of the Included Systematic Reviews

Review	Reported Results					
	All cause mortality	Any vascular death	Non vascular death	Major coronary events	Major vascular events	Total CVD
<b>CTT 2012 and 2015</b>	ARR NNT	ARR NNT	ARR NNT	ARR NNT	ARR NNT	ARR NNT
Overall	RR 0.91 (CI 0.85-0.97) 0.0009 1111	RR 0.85 (CI 0.77-0.95) 0.0006 1667	RR 0.97 (CI 0.88-1.07) 0.001 10000	RR 0.71 (CI 0.65-0.77) 0.0027 370	RR 0.75(CI 0.70 to 0.80) 0.0040 250	
Stratified by baseline risk:						
<5%	RR 0.94 (CI 0.71-1.26) 0.0003 3333	RR 0.80 (CI 0.43-1.47) 0.0002 5000	RR 1.13 (CI 0.76-1.69) 0.0003 -3333	RR 0.59 (CI 0.37-0.96) 0.0008 1250	RR 0.61 (CI 0.45-0.81) 0.0018 556	
≥5% to <10%	RR 0.83 (CI 0.69-0.99) 0.0016 625	RR 0.75 (CI 0.55-1.04) 0.0008 1250	RR 0.87 (CI 0.67-1.11) 0.0007 1429	RR 0.58 (CI 0.48-0.72) 0.0033 303	RR 0.66 (CI 0.57-0.77) 0.0051 196	
≥10% to < 20%	RR 0.88 (CI 0.76-1.02) 0.0020 500	RR 0.84 (CI 0.67-1.05) 0.0009 1111	RR 0.94 (CI 0.76-1.15) 0.0007 1429	RR 0.78 (CI 0.65-0.93) 0.0032 313	RR 0.82 (CI 0.72-0.93) 0.0046 217	
≥20% to < 30%	RR 1.06 (CI 0.86-1.32) 0.0040 -250	RR 0.97 (CI 0.72-1.32) 0.0002 5000	RR 1.13 CI 0.81-1.57) 0.0032 -313	RR 0.80 (CI 0.60-1.06) 0.0066 152	RR 0.81 (CI 0.65-1.01) 0.0088 114	
≥30%	RR 0.94 (CI 0.70-1.25) 0.0068 147	RR 0.88 (CI 0.59-1.33) 0.0063 159	RR 1.07 (CI 0.68-1.69) 0.0020 -500	RR 0.76 (CI 0.50-1.17) 0.0112 89	RR 0.83 (CI 0.58-1.18) 0.0087 115	
Stratified by gender:						
Men					RR 0.72 (CI 0.66-0.80) 0.0060 167	
Women					RR 0.85 (CI 0.72-1.00) 0.0010 1000	
<b>Mora et al. 2010</b>						
Stratified by gender:						
Women	RR 0.78 (CI 0.53 -1.15) 0.0045 223			RR 0.63 (CI 0.49- 0.82) 0.0081 123		RR 0.63 (CI 0.49- 0.82) 0.0081 123
<b>Ray et al. 2010</b>						
Stratified by inclusion criteria:						
Including diabetes trials	Random effects model RR 0.91 (CI 0.83-1.01) 0.0031 321 Fixed effects model RR 0.93 (CI 0.86-1.00) 0.0031 321					
Excluding diabetes trials	Random effects model RR 0.92 (CI 0.84-1.02) 0.0027 371 Fixed effects model RR 0.94 (CI 0.86-1.01) 0.0027 371					

## 4.4 Discussion

### 4.4.1 Principal Findings

Three SRs were included in this overview reporting a mix of aggregate and IPD data and a range of reporting based on gender and baseline cardiovascular risk. The main outcomes reported were all-cause mortality, vascular and non-vascular deaths, and the composite outcomes of total CVD events, major coronary events and major vascular events. CTT reported a significant reduction in all-cause mortality, but no significant reductions were found in the two other systematic reviews for this outcome. Though point estimates are very similar, the difference in statistical significance may be due to the numbers of participants included in each analysis, suggesting an issue with statistical power. It may be the case that the smaller analysis did not have sufficient statistical power though, conversely, it can be argued that when an analysis includes very large numbers, minimal clinical effects can reach statistical significance (Hair et al., 2006, Figueiredo Filho et al., 2013). However, when CTT stratified results by baseline risk profile, non-significant reductions were reported for all-cause mortality in all but one level of risk. As noted, the overall reduction in any deaths reported in the reviews includes participants, who although categorised as ‘primary prevention’, may include those who are risk equivalent to people with established vascular disease, such as people with diabetes and chronic kidney disease. Because of this limitation, arguably the results relevant to low-risk people are those specific to their baseline risk category (<5%, ≥5% to <10%), rather than the aggregate results reported.

In an attempt to specify risk reductions in the lowest risk people included in the CTT analysis, that is in those for whom statins were not already recommended because of CHD risk equivalence, Abramson et al. (2013) reanalysed data from this review for those whose 5-year risk was <5% and for those whose risk was ≥5% to <10%. He found there was no significant effect on mortality in this group of patients (RR 0.95 (CI 0.86 to 1.04)). However, Abramson et al’s analysis included participants with and without vascular disease. It could be expected that the effect of statins would be seen most clearly in the outcome of vascular deaths. While an overall significant reduction was reported for this outcome by the CTT, non-significant reductions were reported at all levels of risk when stratified by baseline risk profile. Significant reduction in major vascular events and

major coronary events were reported and mixed results for these outcomes when stratified by gender and baseline risk profile. It should be noted, however, that CTT's reporting of the composite outcome major vascular events is an addition to the outcomes pre-specified in their protocol. No stroke outcomes were reported in any of the included SRs except as part of composite outcomes.

#### **4.4.2 Strengths and Limitations of the Overview**

As far as I am aware, this is the first overview of SRs that investigates statins in an exclusively primary prevention population. I synthesised evidence from SRs, which are considered the highest quality evidence for health care interventions. I used a transparent search strategy and followed a published protocol (Byrne et al., 2017) to guide the search, extraction and analysis. I used validated instruments to assess the methodological quality of included reviews. The main limitation of the overview is the need to synthesise evidence from SRs with a mixture of IPD and aggregate outcome data and the high level of overlap of included RCTs across reviews. Some trials are part of two or three of the included systematic reviews, whereas many others contribute only to the results of one systematic review. Therefore, the results of the analysis presented here may be driven mostly by these 'over-represented' populations.

Some relevant reviews may have been excluded from this overview because I could not ascertain the proportion of primary prevention participants within the SR. Only one SR reported on risk of bias of the included trials and, I found some of the R-AMSTAR criteria ambiguous and difficult to answer. In addition, trials that fail to find significant benefit from an intervention are often not published (Murad et al., 2014), and it is possible that, as a result, this overview may be affected by publication bias. As I did not retrieve data from primary trials, I was limited to the information and judgements of the included SR authors. For example, the more recent primary prevention study, HOPE-3, reported significant reductions in composite cardiovascular outcomes for those at 'intermediate risk' (defined as an annual risk of MVEs of approximately 1%) (Yusuf et al., 2016). Inclusion of this trial could have influenced the results reported in the included reviews for those in the intermediate risk category. Two of the included reviews had important methodological issues, notably the absence of clear reporting of search strategy and methods of study selection. This, in fact, is the core definition of a systematic review and warrants consideration of whether the individual included studies were simply reviews,

as opposed to systematic reviews. In addition, the use of the composite outcome major vascular event by CTT was not pre-specified in their 1995 protocol and this change from the original protocol is not acknowledged or justified in the paper, which may introduce bias (Page et al., 2012, Kirkham et al., 2010).

Despite calls to make the provision of clinical trial data a legal, regulatory or ethical requirement (Krumholz, 2015, Lo, 2015), and specifically for the publication of CTT's IPD from statin trials (Krumholz, 2016, Godlee, 2016), CTT's data, as well as much of the data from trials from the other two included reviews, remain unavailable for independent analysis. Thus, the goal of fully informed shared decision making cannot be achieved. In addition, while CTT analyses include data from 'almost all of the relevant randomised trials' (Collins, 2014), members of *The BMJ* expert advisory group on statins stated that they intended to contact the authors of 183 statin trials for additional published and unpublished data (Parish et al., 2015). The inclusion of such data in systematic reviews and meta-analyses may alter reported results. However, though the gaps in the data cannot be overcome, such as the lack of transparency in the primary data, I believe this overview presents to patients and clinicians the best, albeit limited, data available.

#### **4.4.3 Clinical Implications**

Some studies have shown that, in absolute terms, the majority of statins users are in the primary prevention category (Byrne et al., 2018). A higher proportion of women who take statins fall into the primary prevention category than men (Wallach Kildemoes et al., 2015, Byrne et al., 2018), and the distribution of statin prescribing has shifted from secondary to primary prevention particularly among women (Wallach Kildemoes et al., 2012b, Feely and Bennett, 2008, Wallach Kildemoes et al., 2012a). Given the on-going debate on the appropriateness of statin use in primary prevention (Wallach Kildemoes et al., 2015, Godlee, 2014b), it is surprising that so few systematic reviews of exclusively primary prevention data exist. Clinical guidelines do not inform the physician on whether recommended thresholds represent valid demarcation lines in terms of the individual patient (Getz et al., 2004), and decisions to take or prescribe a medicine involve a trade-off between the perceived benefits and harms of that medicine for the individual. This trade-off is particularly salient for low-risk people choosing to take a statin for primary prevention of CVD as the patient often feels healthy and may perceive the medicine as unnecessary, with uncertain benefits and potential side effects. Conversely, it may be the

case that clinicians and patients would desire a reduction in CVD, regardless of how small, if they can tolerate statins. Therefore, for people at low-risk of CVD, it is important that the decision to prescribe or take statins is considered in terms of absolute risk reduction to ensure the potential benefits outweigh the potential harms in the context of that patient's preferences. Unfortunately, some of the gaps in the data I have presented here cannot be overcome. Only one included review stratified patients by risk and gender and one by gender only. The question remains for the clinician; what is the relevant information for the individual patient?

Arguably, clinical decisions should be based on 'hard' endpoints such as cardiovascular death, MI and stroke because these are least subject to bias in adjudication (Abramson et al., 2013). As these outcomes were not reported separately in the overview, 'all-cause mortality' is the most reliable outcome on which to base decisions. The use and reporting of composite outcomes has been criticised as they may be unreasonably combined, inconsistently defined and inadequately reported (Cordoba et al., 2010). Reported risk reductions of composite outcomes may be driven by large reduction in the less serious components of the outcome rather than the more serious. For example, if a composite outcome comprises a larger proportion of 'less serious' outcomes such as angina and revascularisations compared to MIs or stroke, this may result in misleading impressions of the impact of treatment (Mora et al., 2010). Mora et al. analysed the components of the composite outcome 'total CVD events' in women in one large trial included in their review. They found that women had a significant reduction in revascularisations and unstable angina, but not in other components of the composite outcome, including stroke. Patients or prescribers may alter their decision making about the potential benefits of statin use even though larger treatment effects may be associated with less important components (Ferreira-González et al., 2007). Data for each component of each composite outcome in the included reviews were not supplied and some of the meta-analyses included composite outcomes, which may be inappropriate (Cordoba et al., 2010). The details of composite outcomes in the included SRs are described in Appendix 11.

For the individual patient and clinician, there are three considerations in the process of informed decision making. Firstly, what is the relative risk reduction according to the baseline risk of the individual. Secondly, what is the absolute risk reduction in risk for

that person, and, finally, what are potential side effects from taking statins in the context of that patient's preferences.

As I have outlined in this overview, the outcomes reported in the SRs that were stratified by baseline risk or by gender may be the most pertinent to clinical decision making. For example, for a woman whose risk is <5%, which results are relevant? Should she be presented with the relevant non-gender-specific results reported by CTT, such as the overall results for relative reduction in all-cause mortality (RR 0.91 (CI 0.85-0.97)) or the non-significant relative reductions for those at her relevant baseline risk, (RR 0.94 (CI 0.71-1.26))? Or should she be presented with the overall non-significant relative reduction presented by Mora et al. for women (RR 0.78 CI 0.53-1.15)? The same dilemma would arise for a high-risk woman, for example, one whose baseline risk is 30% or greater. In this case the relevant risk reduction reported at her baseline risk was RR 0.94 (CI 0.70-1.25). In a discussion on how to apply results of systematic reviews to patient care, Murad et al. suggest that clinicians consider the upper and lower bounds of confidence intervals (Murad et al., 2014). They can then consider how they would advise their patients were the upper boundary to represent the truth and how they would advise their patients were the lower boundary to represent the truth.

The included SRs reported reductions in risk of CVD outcomes as relative risk reductions, but for an individual patient, knowing their absolute risk reduction is more relevant when making a decision to take a statin (Murad et al., 2014). Sun et al. give a good example of two people for comparison (Sun et al., 2014). One is a 65-year old man who smokes, does not have heart disease but who has high total cholesterol levels and elevated blood pressure. The second is a 45-year old woman who does not smoke, has elevated total cholesterol levels and slightly elevated blood pressure. Based on the ACC/AHA risk calculator, the man has a 38% absolute risk of having a major coronary event in the next ten years; the woman, a 1.4% absolute risk. According to the risk reductions reported by CTT in this overview (Mihaylova et al., 2012), statin therapy would reduce the man's relative risk of major coronary events by 24% and the woman's relative risk by 41%. However, the man could expect an *absolute* risk reduction of about 9 % (Number Needed to Treat of 11), the woman of 0.6% (Number Needed to Treat of 166) (Appendix 12).

Having considered which relative risk reduction is most relevant to the particular individual and the associated absolute risk reduction, the next consideration should be the potential harms from taking statins. Collins et al. have reported that treating 10,000 patients for 5 years would cause about 5 cases of myopathy, 50 to 100 new cases of diabetes and 5 to 10 haemorrhagic strokes. The authors argue that the harmful effects of statin therapy can usually be reversed without residual effect by stopping the statin therapy, whereas ‘harmful effects of heart attacks or strokes that occur because statin therapy has not been used can be devastating’ (Collins et al., 2016). Even if there are side-effects in a lower risk person, they may derive long term benefit by stabilising or slowing the progression of subclinical vascular disease. However, the definition of myopathy, as described by Armitage et al. (Armitage, 2007), may be a high bar for diagnosing muscle symptoms among real people, who may simply define myopathy as any muscle symptom and observational data suggest that the frequency of statin myopathy may be higher (Buettner et al., 2008, Fernandez et al., 2011). Indeed, there is a large difference between the quantification of muscle side effects between Collins et al. and Buettner et al., the former reporting five cases of myopathy per 10,000 treated patients over five years, the latter, a difference of 5.3% between statin and placebo groups, which is the equivalent of 530 cases of ‘musculoskeletal pain’ per 10,000 patients treated. Thus, the estimates vary by a factor of 100.

However, a recent systematic review of observational studies on statins use and new-onset diabetes noted that this association may be limited due to ‘indication bias’ (Strom, 2006); that is, the risk of an adverse event is related to the indication for medication use but not the use of the medication itself. In an observational study one can only observe the effect of an exposure, in this case to statins. Groups are not randomly assigned to treatment or placebo groups. Therefore, observational studies are much more vulnerable to confounding bias and their results may be less robust than those of a randomised controlled trial (Jepsen et al., 2004). For example, pre-diabetes, the most important risk factor for type 2 diabetes, is associated with dyslipidaemia and this increases both the chances that people with pre-diabetes will be treated with statins and that these subjects will develop type 2 diabetes (Casula et al., 2017). Moreover, those with type 2 diabetes are considered risk equivalent to those in the secondary prevention category and their

treatment with statins recommended by clinical guidelines (Catapano et al., 2016). Consideration of the potential risk of developing type 2 diabetes *from* statin use is complex. The small risk of developing diabetes may be favourably balanced by the cardiovascular benefit (Sattar et al., 2010). In addition, although those with diabetes have a higher cardiovascular event rate than those without, it may be the case that the event rate in those with new-onset diabetes is lower than those with established diabetes at baseline (Waters et al., 2011). This would strengthen the argument that any potential risk of new-onset diabetes is outweighed by the lowering of cardiovascular risk.

A recent systematic review by Albarqouni et al. attempted to quantify the minimum acceptable risk reduction that patients say is necessary to justify a daily intake of medication to prevent CVD events (Albarqouni et al., 2017). My analysis of those considered *low*, *medium*, *high* and *very high* risk according to the most recent 2016 guideline found that only some of those at *high* or *very high*-risk would reach an acceptable level of risk reduction to justify taking a medicine for life (Byrne et al., 2019). In addition, Albarqouni et al. reported that in one study only 3% of community living older people would agree to CVD preventative medicines if that medication had adverse effects that could affect their activities of daily living and half would not agree to take the medication if it was associated with even mild fatigue or nausea (Byrne et al., 2019).

#### **4.4.4 Comparison with Other Studies**

I am aware of only one other overview of systematic reviews on the topic of statins for the primary prevention of CVD by Karmali et al. (2016). This overview considered drugs, including statins, for the primary prevention of CVD and reported statistically significant reductions in the risk of CVD for statins RR 0.75 (CI 0.70 to 0.81). The Karmali overview included three of the four reviews from my overview (Mihaylova et al., 2012, Fulcher et al., 2015, Ray et al., 2010). However, no attempt was made to disaggregate exclusively primary prevention data and therefore it cannot be compared with my overview.

## **4.5 Conclusion**

This overview suggests there is mixed evidence on the effectiveness of statins in primary prevention populations. However, this population is heterogeneous with widely ranging baseline risks. For the individual patient and clinician, there are three considerations in the process of informed decision making. Firstly, what is the relative risk reduction according to the baseline risk of the individual? Secondly, what is the absolute risk reduction in risk for that person, and, finally, what are potential side effects from taking statins in the context of that patient's preferences? The gaps in the data, outlined in this overview, cannot be overcome without patient-level data being made available for independent analysis. However, this overview clearly elucidates the information that is available at present allowing patients and clinicians to know that this is the best, albeit limited, data available.

# **5 Statins for the Primary Prevention of Cardiovascular Disease: A Simulation of Eligibility, Costs, Patient Preferences and Number-needed-to-treat in the Context of Changing Clinical Guidelines**

## **5.1 Introduction**

To date, clinical guidelines and cost-effectiveness studies have broadly supported the widening use of statins in low-risk people and recent analyses have found statins to be cost-effective in primary prevention (Heller et al., 2017, Mc Connachie et al., 2013). However, the tolerability and safety of statins or the views of patients on life-long drug therapy are not considered in such analyses and, in the context of the widespread use of statins, particularly in low-risk people, are important and relevant issues (Taylor et al., 2013). Accounting for even modest estimates of the disutility caused by daily medication use could negate the benefit of statins and result in net harm to low-risk people rather than net benefit (Heller et al., 2017). In short, a major caveat exists about the widespread use of statins in primary prevention in terms of acceptability to patients and benefit to society.

Decisions to take or prescribe a medicine involve a trade-off between the perceived benefits and harms and is particularly salient for those choosing to take a statin for the primary prevention of CVD as the patient often feels healthy and may perceive the medicine as unnecessary, with uncertain benefits and potential side effects (Albarqouni et al., 2017). Various methods to aid the decision-making of the individual patient and clinician now exist (Polak and Green, 2015, Trevena et al., 2006, Bonner et al., 2014, Trevena, 2014) such as the ‘number-needed-to-treat’ (NNT), that is, the number of patients that must be treated to prevent one additional adverse outcome (death, stroke, etc.) over a specified time period (Chatellier et al., 1996).

The overarching aim of this chapter is to explore the impact of changing clinical guidelines on statins for prevention of cardiovascular events over time incorporating patient preferences regarding preventive treatments. This involved four analyses. Firstly,

I estimated the increasing proportions of people who would be considered eligible for statin treatment according to each of seven European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines from 1987 and 2016. Secondly, I estimated the potential cost increases associated with each consecutive guideline recommendation. Thirdly, I calculated the NNT to prevent one major vascular event in patients at the lowest baseline risk for which each guideline recommends treatment, as well as for those at *low*, *medium*, *high* and *very high* risk according to the most recent 2016 guideline. Finally, I compared these NNTs with those reported by patients as being the minimum benefit they would need to justify taking a daily medicine (Albarqouni et al., 2017).

## **5.2 Methods**

### **5.2.1 Sample**

The sample comprises nationally representative, community dwelling participants aged over 50 years from The Irish Longitudinal Study on Ageing (TILDA), who had no reported prior history of CVD (n=4,513) (Appendix 13). TILDA collects health-related and socio-demographic data on a nationally representative sample of community living adults aged 50 years and older in Ireland and the sample in this study was based upon my previous secondary analysis of these data (Byrne et al., 2018).

### **5.2.2 Time Trends in Eligibility for Statins for Primary Prevention**

Each clinical guideline describes cholesterol thresholds that may warrant statin treatment, depending on a person's baseline risk. Using these thresholds, I calculated the proportion of the TILDA sample that would be considered eligible for statin therapy. While these guidelines often recommend a trial of lifestyle changes to lower cholesterol levels before prescribing, for the purpose of this analysis, I assumed treatment thresholds above which statins would be prescribed based on each of the guidelines (Appendix 14).

### **5.2.3 Cost Increases Due to Widening Eligibility**

I used cost data from June 2016, to reflect the type, dosages and frequency of statins reimbursed through the General Medical Service (GMS) in Ireland. I estimated a weighted average annual cost per patient taking statins of €149.33. The population in Ireland over 50 years is 1,446,460 and based on a previous study of TILDA, I estimate

that 81% of these do not have prior CVD (n=1,171,326) (Byrne et al., 2018). The total cost of statins was calculated by multiplying the estimated weighted average annual cost per patient by the estimated population of interest. Uncertainty was explored using a Monte Carlo simulation process, in which the proportions and units costs were assigned appropriate probability distributions, and 1,000 replications of the total cost were generated to estimate 95% confidence intervals for the total cost estimates (Appendices 15 and 16).

#### **5.2.4 Changes in Numbers-Needed-to-Treat due to Treatment Threshold Changes**

Each clinical guideline defines baseline risk levels above which treatment with statins could be recommended, depending on the individual's cholesterol levels. For example, in the 2016 guideline, a *low-risk* person whose baseline risk is less than 1% could be recommended for statins if their LDL was greater than 4.9 mmol/L. Thus, all *low-risk* people would not be eligible for treatment, only those with LDL above 4.9mmol/L. However, as some *low-risk* people could be eligible, I defined 1% as the lowest level of risk for the purposes of calculating the NNT.

In 1994 and 1998 the guidelines recommended use of the Coronary Risk Chart to assess a person's baseline risk of a *fatal or non-fatal* CVD event and the lowest risk that could be recommended statins was 20%. From 2004, the SCORE risk assessment tool was recommended to assess a person's baseline risk of *fatal* CVD event. Thus, the risk bands used in this analysis may seem low to those more familiar with other risk assessment tools such as QRISK, which estimate a person's risk of *fatal and non-fatal* CVD. Anyone whose baseline risk of a *fatal* CVD event is greater than or equal to 5% is considered 'high risk' according to SCORE, whereas anyone whose baseline risk of a *fatal or non-fatal* CVD event is greater than 20% is considered 'high risk' according to QRISK. The lowest risk that could be recommended statins in 2004 and 2007 was 5% and in 2012 and 2016, less than 1%. Because two different types of risk assessment tool were used in the guidelines, it was necessary to equalise (Appendix 17).

I assumed that taking statins reduced a person's risk of 'major vascular events' by 25% ((RR 0.75 (CI 0.70-0.80)) (Mihaylova et al., 2012), and estimated the NNT to prevent one event for those at the lowest risk for which each guideline recommends treatment

(Appendix 18). I also calculated the NNTs for those considered *low*, *medium*, *high* and *very high* risk according to the most recent EAS/ESC guidelines (Catapano et al., 2016) (Appendix 19).

### **5.2.5 Numbers-Needed-to-Treat and the Patient Perspective**

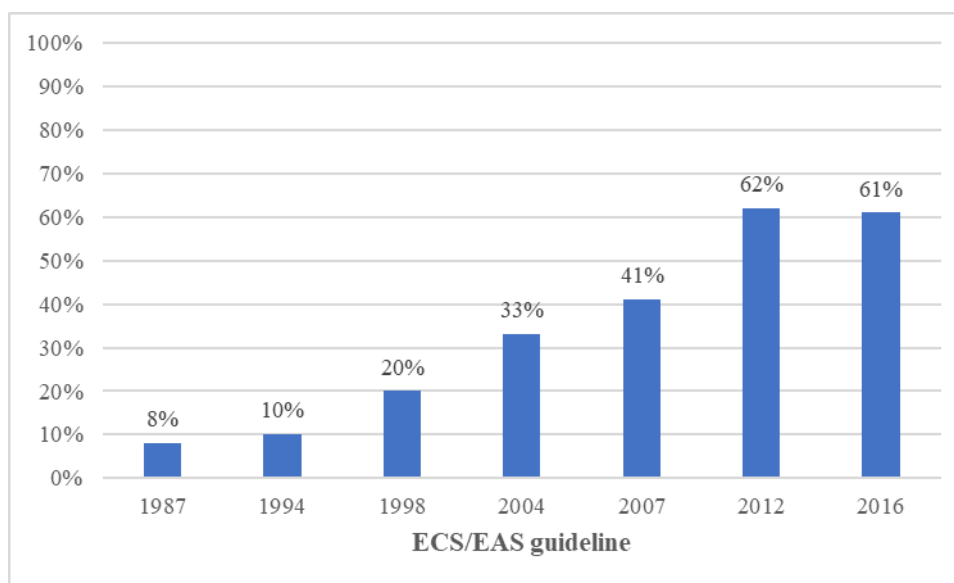
I considered the NNTs estimated above in the context of a systematic that reported on the minimum acceptable risk reduction that patients say is necessary to justify a daily intake of medication to prevent CVD events (Albarqouni et al., 2017). Acceptable NNTs were reported in this review in terms of five-year NNTs, and it was necessary to convert each person's baseline 10-year risk to the equivalent five-year risk (Appendix 20). A wide variation in this preference was reported; between 46% and 87% (average 71%) of participants would consider taking a medication with an  $NNT \leq 30$ . For illustrative purposes only, I use the  $NNT \leq 30$  as a proxy for acceptability of taking statins for life and assume that an  $NNT > 30$  is not acceptable to any patient (Appendix 21 and Appendix 22).

## **5.3 Results**

### **5.3.1 Time Trends in Eligibility for Statins for Primary Prevention**

In 1987, approximately 8% of the sample group would have been eligible for statin therapy, and by 2016, 61%; an increase of 663% in eligibility. As the characteristics of the sample remained the same, changes in eligibility for statin therapy are due to changes in treatment thresholds of the guidelines and not changes in the sample (Figure 5.1).

Figure 5.1: Proportion of Participants Eligible for Statin Therapy According to Changes in ESC/EAS Clinical Guidelines



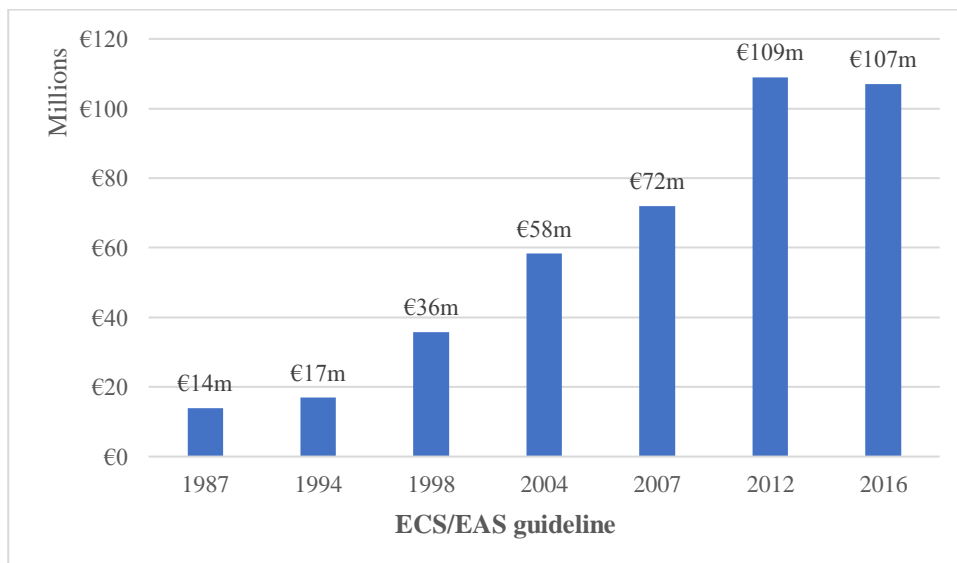
### 5.3.2 Cost Increases due to Widening Eligibility

Assuming that all those eligible take statins according to each guideline, the overall national cost would increase from €13.9m in 1987 to €107.1m in real terms (2016 prices), including both public and private expenditure on statins (Table 5-1 and Figure 5.2).

Table 5-1: Proportion of Participants Eligible for Statin Therapy According to Changes in ESC/EAS Clinical Guidelines and Associated Cost Implications

Year of Clinical Guideline	Proportion of Statin-Eligible (SE)	Cost	Cost CI
Guideline 1: 1987	7.95% (0.33%)	€13,902,610	(€12,668,710 - €15,045,833)
Guideline 2: 1994	9.68% (0.44%)	€16,924,364	(€15,364,264 – €18,456,889)
Guideline 3: 1998	20.46% (0.60%)	€35,767,583	(€33,583,491 - €37,922,496)
Guideline 4: 2004	33.33% (0.70%)	€58,256,655	(€55,808,914 - €60,866,411)
Guideline 5: 2007	41.14% (0.73%)	€71,918,939	(69,140,111 - 74,850,412)
Guideline 6: 2012	62.33% (0.72%)	€108,959,843	(€106,127,604 - €112,017,290)
Guideline 7: 2016	61.27% (0.73%)	€107,100,599	(€104,314,514 - €110.061,679)

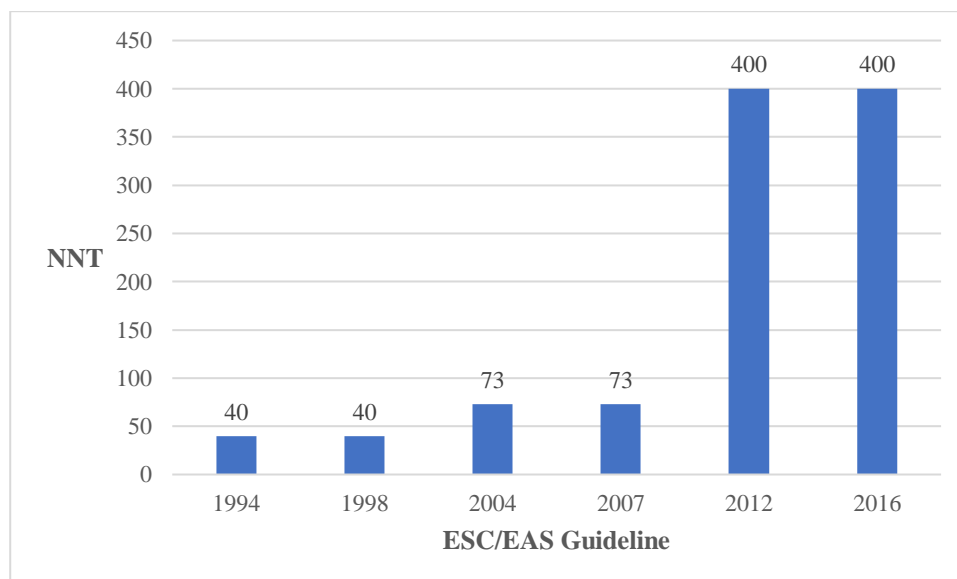
Figure 5.2: Associated Cost Implications of Changes in ESC/EAS Clinical Guidelines



### 5.3.3 Changes in NNT Due to Treatment Threshold Changes

The NNT to prevent one major vascular event in those at the lowest levels of risk for which statins could be recommended was 40 according to the 1994 and 1998 guidelines; 73 according to the 2004 and 2007 guidelines; and 400 according to the 2012 and 2016 guidelines (Figure 5.3).

Figure 5.3: NNT for those at the Lowest Baseline Risk for which Statins could be Recommended According to ESC/EAS Guidelines for the Prevention of CVD



400 *low-risk* people would have to be treated in the group to prevent one major vascular event, between 53 and 400 *moderate-risk* people, between 25 and 53 *high-risk* people and 25 or fewer *very high-risk* people (Table 5-2).

Table 5-2: NNT to Prevent One Major Vascular Event for Each Sample Profile

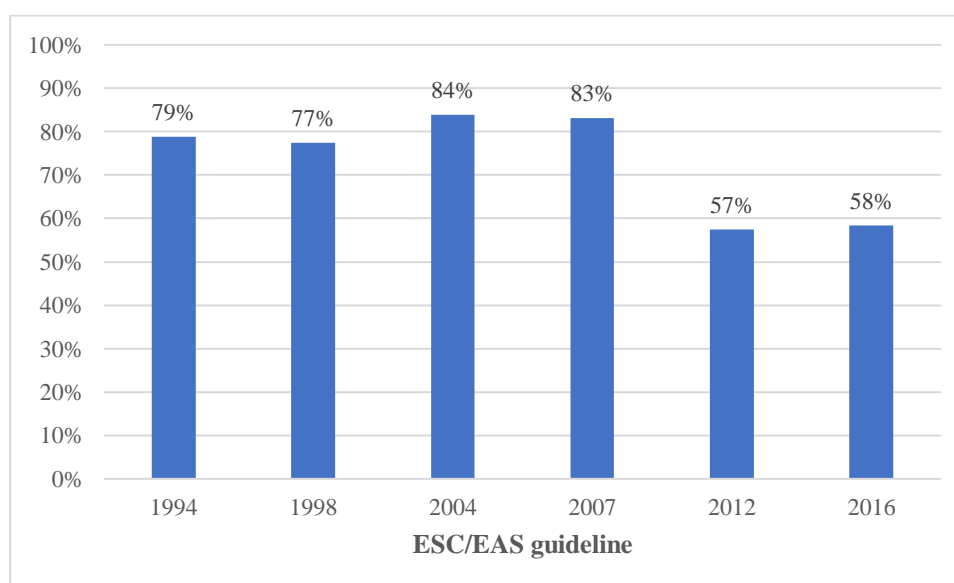
Absolute five-year risk of fatal and non-fatal CVD events*	Relative risk reduction in major vascular events from taking statins (RR)**	Absolute risk reduction of major vascular events from taking statins	NNT
<b>Low-risk</b> <1%	0.75 (0.70 – 0.80)	<0.25%	400 or more
<b>Moderate risk</b> ≥1% to <7.5%	0.75 (0.70 – 0.80)	≥0.25% to <1.9%	400 to 53
<b>High risk</b> ≥7.5% to <16%	0.75 (0.70 – 0.80)	≥1.9% to <4%	53 to 25
<b>Very high risk</b> ≥16%	0.75 (0.70 – 0.80)	≥4%	25 or less

Notes: \* See Appendix 20. \*\* RR reported for the outcome ‘Major Vascular Events’ as reported in: Cholesterol Treatment Trialists C, Fulcher J, O’Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397-405.

### 5.3.4 Numbers-Needed-to-Treat and the Patient Perspective

The proportion of people recommended for treatment who would reach an NNT ≤ 30 was 79% in 1994, rising to 84% in 2004 and falling to 58% in 2016 (see Figure 5.4).

Figure 5.4: Proportion of those Eligible for Statins who are Above the Acceptable NNT Needed to Justify Taking a Daily Medication



However, as Albarqouni et al. reported in their systematic review, there is a wide range in the proportion of people who would find this NNT acceptable; between 46% and 87% (average 71%). Therefore, on average, the proportion of those who are eligible for statins and who would find this NNT as an acceptable trade-off for taking a medicine for life falls from 56% in 1994 to 41% in 2016 (Appendix 23).

Only some of those classified as *high* and *very high-risk*, according to the 2016 EAS/ESC guidelines, would reach an acceptable NNT of less than 30 (Appendix 23).

## 5.4 Discussion

Changes in clinical guideline recommendations have resulted in more than a 600% increase in statin eligibility for primary prevention with 61% of the cohort becoming eligible for statin therapy by 2016, with significant cost implications. While 61% may be eligible based on guideline criteria, this does not necessarily represent the actual proportion of this patient population who are taking statins. Indeed, my previous analysis found that only 30% of the TILDA cohort took statins (Byrne et al., 2018) and adherence to statins in real-life is reported to be, on average, 50% (Lemstra et al., 2012). However, the purpose of this chapter is to illustrate the *potential* impacts of widening statin eligibility based on changing guidelines over time.

Debate has ensued about clinical guideline recommendations (Greenland and Bonow, 2016, Redberg and Katz, 2016, Unruh et al., 2016), which have tended to expand the number of people eligible for treatment, without explicitly considering the adverse impacts of such measures (Moynihan et al., 2013, Unruh et al., 2016). For example, a UK study found that if a new risk threshold were used, almost all of their sample would be indicated for statin treatment compared to less than three quarters, were the previously recommended risk threshold used (McFadden et al., 2015). A US study found that almost half of those currently not on statins would be recommended for statin treatment according to new guidelines; the largest potential change was in those without CVD or diabetes (Schoen et al., 2015).

However, for many of the individuals, the reduction in risk of a cardiovascular event would not be large enough to justify taking a daily medication. Using the most conservative estimate, half of all those taking statins for primary prevention would not find it acceptable to take a statin for life. Using the least conservative measure, less than one third of this patient population would find taking statins acceptable.

In my analysis I assumed that the relative risk reduction from taking statins was similar across sub-groups. However, when stratified by gender, smaller non-significant reductions in major vascular events were reported for women (Fulcher et al., 2015), which would further reduce acceptability. The evidence supporting statin use in older people is mixed (Petersen et al., 2010, Roberts et al., 2007, Savarese et al.) and should also be considered in terms of acceptability for this group. Albarqouni et al. reported that in one study only 3% of community living older people would agree to a medication with adverse effects that could affect their activities of daily living and half would not agree to take the medication if it was associated with even mild fatigue or nausea. Studies have found that statin use can be associated with an increased risk of myopathy, rhabdomyolysis, diabetes and haemorrhagic stroke (Collins et al., 2016), although debate has ensued as to the prevalence and significance of such adverse effects (Krumholz, 2016).

The implications of these findings are that pharmacoeconomic evaluations and clinical practice guidelines, as currently conducted, may not be sufficient to evaluate the value of statin therapy and recommend appropriate usage. There have been calls to incorporate evidence from sources other than conventional clinical trials into the development of clinical guidelines, including the views and experience of those using the intervention (Wieringa et al., 2018). Cost-effectiveness analyses have sometimes, albeit rarely, included NNT ratios and this may increase the understanding and relevance of such publications for prescribers and patients (Garg et al., 2013). It can be seen that a patient's preference for taking a daily pill is an important factor in assessing whether statin use represents net benefit. The consideration of such preferences should be incorporated into future CEAs and clinical guidelines.

## 5.5 Strength and Limitations

This study is the first I am aware of to simulate the effect of evolving guidelines over a thirty-year period and can inform the debate on appropriate prescribing. The study has some limitations; I assumed that statin therapy was initiated at certain thresholds, even though some of these patients may be recommended life-style changes rather than statin therapy. The estimation of baseline risk within the TILDA sample was complex. Some of the sample may have already been taking statins and therefore their original baseline risk would have been higher and the risk estimated for the current study may underestimate this original baseline risk as their cholesterol is now well controlled. I did not assess the changes in types of statins, dosage or generic substitution over the period considered and, in the absence of patient level data relating to type and dosage of statin, I employed an estimated average unit cost. All estimates in the cost analysis were presented in real terms based on 2016 prices which, while medical inflation has not been significant, may not reflect current prices. Finally, the estimates relating to patient preferences were based on a published systematic review. This review found that the assessment methods used to examine patient preferences were heterogeneous with a wide variety of estimates reported. Therefore, an accurate quantitative summary estimate of the minimum acceptable risk reduction could not be calculated and I used  $NNT \leq 30$  as a proxy for acceptability of taking statins for life for illustrative purposes only.

It is important to point out that each of the four sections of this chapter would require much more detailed analysis to ascertain the real-world impacts of widening eligibility for statin use. In addition, the generalisability of these findings may be limited, since they are based on a study of one country. The sample used was nationally representative of the Irish population aged 50 years or over and the costs based on reimbursement data from Ireland. The patient preferences were taken from a systematic review of patient preferences, which included studies from many countries. It is possible that patient preferences differ in individual countries according to social and cultural norms. In addition, prescribing, insurance and reimbursement practices, as well as drug costs, will differ from country to country. However, I believe that my analysis offers an important and original insight to inform decision making in clinical practice and policy.

## 5.6 Comparison with Existing Literature

As noted above, this study is the first of which I am aware that has examined the influence of changing clinical guidelines over a thirty year period. However, other studies have considered the impacts of single changes to guidelines, both in Europe and the US. For example, McFadden et al. (2015) estimated numbers affected by changes in 2014 to UK guidelines for statin use in primary prevention of cardiovascular disease. The guidelines had previously recommended that statin treatment was indicated for those whose baseline risk exceeded 20% (QRISK), but the new guidelines recommended that those whose risk exceeded 10% now be considered for treatment. The authors estimated that 58% of men and 55% of women would be indicated for treatment by five years and 71% of men and 73% of women by ten years using the 20% threshold. Using the proposed threshold of 10%, 84% of men and 90% of women would be indicated for treatment by 5 years and 92% of men and 98% of women by ten years.

Ueda et al. (2017) determined risk factor levels required to exceed the risk threshold for statin therapy, and to estimate the number of adults in England who would require statin therapy under these new guidelines. They found that ‘even with optimal risk factor levels, males of different ethnicities would exceed the 10% risk threshold between the ages of 60 and 70 years, and females would exceed the threshold between 65 and 75 years. Under the NICE guidelines, 11.8 million males and females (37% of the adults aged 30–84 years) would require statin therapy, most of them (9.8 million) for primary prevention. When analysed by age, 95% of males and 66% of females without CVD in ages 60–74 years, including all males and females in ages 75–84 years, would require statin therapy.’

Schoen et al. (2015) reported that changes to treatment guidelines from 2001 Adult Treatment Panel III (ATPIII) to 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines would expand the number of patients recommended to receive statins, particularly among patients who were previously thought to be at moderate risk, and would increase the intensity of treatment for many patients at high risk. (Abramson and Wright, 2007) quantified this increase, noting that the changes ‘increased the number of Americans for whom statins are recommended from 13 million to 36 million, most of whom do not yet have but are estimated to be at moderately elevated risk of developing coronary heart disease’.

## **5.7 Implications for Research and/or Practice**

Changes in recommendations for the use of statins would result in almost two thirds of over-50s in Ireland and similar countries being considered eligible for statin therapy. This has implications for the medicalisation of large proportions of our population, as well as for already resource constrained healthcare budgets. The value-or-money of the widening use of statins should be considered from both a societal and individual perspective. The decision to take and reimburse statins could be informed by NNTs, which are large in some risk categories. As seen from the analysis in this chapter, a proportion of the sample would require significantly greater reductions in absolute risk to justify taking a daily medication. The patient's decision to take statins should be considered in the context of shared decision-making and the relevant NNT so that informed choices can be made relevant to their individual baseline risk.

# **6 Medicalisation, Risk and the Use of Statins for Primary Prevention of Cardiovascular Disease: A Scoping Review of the Literature**

## **6.1 Introduction**

The term ‘medicalisation’ refers to problems that have moved into the medical jurisdiction and this process has long been the focus of much social science analysis (Conrad et al., 2010). To be medicalised, issues must first be subject of the ‘medical gaze’ (Foucault, 2002, p.24) and become defined and constructed as medical problems requiring a medical solution (Williams et al., 2011). Understandings of the nature of disease and medicine are not static and are ‘culturally, spatially and historically specific’ (Klawiter, 2004). Thus, a ‘regime of truth’ (Wilson and Prior, 2017) emerges and becomes dominant along with a particular medical vocabulary and ideology that are used to order and define the medical problem (Halfmann, 2011). The process of medicalisation occurs on three levels. Firstly, it occurs conceptually, ‘when a medical vocabulary is used to define a problem’, secondly, institutionally, ‘when medical professionals legitimate a ... problem’ and thirdly, ‘on the level of the doctor-patient interaction, when the actual diagnosis and treatment of a problem occurs’ (Gabe and Calnan, 1989). To date, debate around medicalisation in the context of specific diseases has almost exclusively revolved around the appropriateness of the use of psycho-social or ‘lifestyle’ medicines. Examples include the treatment of sexual and sleep disorders, social anxiety, hyperactivity, attention difficulties and depression with drugs (Abraham, 2010). In contrast to these areas of medical intervention where the benefit of drugs is disputed, cardiovascular disease (CVD) is deemed to be the leading cause of death worldwide (World Health Organization, 2017) and ‘the stakes are high’ in its prevention (Pollock and Jones, 2015).

One of the most significant shifts in modern medicine has been the shift from a reactive to a preventative model of healthcare (Radley, 1994 cited in Farrimond et al., 2010), which was described over twenty years ago by Skolbekken (1995) as an emerging ‘risk epidemic’. In the context of CVD prevention, this has facilitated the process of medicalisation predicated on healthy individuals who have risk factors for CVD being subject to surveillance and their ‘risk state’ becoming ‘more embodied and, ... more

disease-like' (Aronowitz, 2009). Skolbekken contended that crucial to the emergence of this risk epidemic was the statistical epistemological paradigm of scientific medicine and various tools from which it originated. These tools include the development of scientific thinking to include uncertainty, the use of risk calculations, the introduction of randomised control trials and clinical epidemiology, and the development of risk analysis. However, overarching all of these tools and techniques is an 'ideological background wherein the application of these techniques become legitimate' (Skolbekken, 1995). Arguably, the management of risk has become a dominant feature of contemporary medicine whereby healthy people, with no symptoms of disease perceptible either to themselves or their doctors, often receive a diagnosis of disease.

Risk and preventative health in the context of CVD have most notably been associated with the Framingham Study conducted in the mid twentieth century, the first major study to examine the 'modern epidemic' of coronary heart disease (Greene, 2007, p.2). As mortality and morbidity from infectious disease fell, heart disease emerged as the foremost killer of modern times and investigators began to single out 'prepathological' factors that eventually became known as coronary risk factors (Greene, 2007, p.2). The monitoring of one such risk factor, blood cholesterol levels, is central to the contemporary management of CVD risk and a person's low-density lipoprotein (LDL) cholesterol level is considered a surrogate for cardiovascular events (Weintraub et al., 2015). While this surrogate marker may be a 'true' risk factor, conversely it may simply be a bystander 'without an active role' (Yudkin et al., 2011). Nonetheless, a key characteristic of the transformation of risk into a chronic condition is the imperative to 'know your numbers' and treat 'to target' (Moynihan, 2011). These numbers will by their nature be distributed along a continuum where one extreme represents a level of abnormality that justifies treatment. The problem is that:

... a combination of vested interest and good intentions produces continual pressure to extend the range of abnormal, shifting the demarcation point into the territory previously considered normal (Heath, 2013).

Simply feeling well is no longer sufficient confirmation of good health, and this 'growing irrelevance of the symptom' (Greene, 2007, p.9) has led to 'the experience of being at

risk for disease ... converging with the experience of disease itself' (Aronowitz, 2009). This type of disease experience has no relationship with symptoms but is connected to a statistical likelihood, or probability, of developing symptoms at some point in the future (Greene, 2007). Thus, 'probabilistic thinking' comprising the use of empirical observational data to forecast 'real-life outcomes which are too complex to be precisely predicted' (Heyman et al., 2013) plays a key role in how people think about and perceive risk. Indeed, it is argued that health has been *redefined* as risk reduction (Dumit, 2012). Jutel and Nettleton (2011) describe how diagnosis:

organises a disease, providing a name, a treatment, a direction to an ailment. It is an interpretative project involving back and forth between lay and professional to find a satisfactory explanation. And diagnosis can be a narrative surrender, where a lay person's story of embodied experience is reappropriated, and recast by medicine.

In this way, the 'line between the normal and the pathological ... (has become) ... a numerical abstraction' (Greene, 2007, p.xi) and for many people, this shifting demarcation line leads to the prescription of a drug.

Risks without consensus nor links to authority, such as the medical profession, may fail to become legitimate (Brown, 2014) and the rationale for taking action is motivated by socially accepted contingencies that concern particular social groups (Heyman et al., 2013). In the context of CVD, the link between cholesterol and CVD is seen as a 'generally accepted truth' by health professionals and the lay public (Hann and Peckham, 2010) and statins are the 'main approach used' for lowering cholesterol levels (Hann and Peckham, 2010). However, while the expertise of medical professionals is grounded in their technical knowledge, 'the communication of such knowledge forms the basis of informed consent' (Heyman et al., 2013, p.6). The public will 'calibrate the personal value of outcomes', setting their own acceptable levels for tolerating risk, while drawing on the professional's assessment of probability of those outcomes (Heyman et al., 2013, p.6). Thus, '(r)isk should be seen as a joint product of *knowledge* about the future and *consent* about the most desired prospects' (Douglas & Wildavsky, 1982, cited in Brown, 2014).

I contend that the use of statins for primary prevention of CVD exemplifies the medicalisation process predicated upon a broad societal consensus that high cholesterol is a legitimate risk requiring medical intervention. There have been calls to analyse medicalisation at the micro-level of specific disease (Carter et al., 2015). The scoping review presented in this chapter responds to these calls by focusing on what the literature reveals about the specificities of medicalisation and the social construction of the ‘at risk’ state associated with the use of statins for primary prevention of CVD.

## **6.2 Methods and Aims**

This review comprises a broad scoping review. The purpose of a scoping review is to ‘determine the scope or coverage of a body of literature on a given topic and give clear indication of the volume of literature and studies available as well as an overview (broad or detailed) of its focus’ (Munn et al., 2018). In contrast to a systematic review, scoping reviews have a broader scope with ‘correspondingly more expansive inclusion criteria’ (Munn et al., 2018).

The main aim of this review is to provide an overview of the qualitative research literature on patients’ and doctors’ perceptions and reported behaviours about statin therapy, particularly in primary prevention of CVD. In addition, I aimed to identify what types of studies were available on the topic, to clarify the relevant key concepts, and to identify gaps in the knowledge base (Munn et al., 2018). The review was guided by the following research questions:

1. How is preventative health and risk perceived and medicalised in the context of primary prevention of CVD?
2. How is candidacy for statin therapy perceived, negotiated and socially constituted?
3. On what assumptions about risk, high cholesterol and statins are these perceptions and negotiations of statin candidacy based?
4. Is there evidence of socio-demographic or cultural differences in these perceptions and negotiations of statin candidacy?

### **6.3 Inclusions and Exclusion Criteria and Search Strategy**

I included articles if they comprised analyses of interviews or focus groups with clinicians who prescribe or members of the public who take, refused to take or discontinued statins for the prevention of CVD that were published in peer-reviewed journals. I also included systematic reviews of interviews or focus groups. While the review is limited to studies that used the method of interviews or focus groups, a variety of different methods were employed in these included studies informed by diverse epistemological and theoretical standpoints. Articles were excluded if they were published before 2000, as I hypothesised that attitudes and perceptions of doctors and patients may differ in more recent years than in the earlier years of statin prescribing. I excluded any studies that focused on the impact of interventions to improve adherence to statins, or that focused on familial hypercholesterolaemia, terminal illnesses or secondary prevention of CVD. However, if articles were unclear regarding whether the use of statins was for primary or secondary prevention or did not differentiate between them, they were included. In addition, I excluded articles that focused solely on patients' or doctors' attitudes regarding diet or lifestyle interventions designed to reduced CVD risk. I also excluded articles that comprised opinions of the authors rather than original research. I excluded articles based on surveys and questionnaires, as I hypothesised that these would not yield the type of data I required to guide the in-depth interviews I planned on conducting.

A three-step search strategy was undertaken in this review. Firstly, I identified relevant MeSH and Emtree terms, combinations of which were used in the relevant databases. These search terms included *statins; hydroxymethylglutaryl-CoA reductase inhibitors; cholesterol; attitudes; beliefs; opinions; drug usage attitudes; decision making; research qualitative; risk reduction behavior; social norms; ethnology; behavioural intention; planned behavior; choice behavior; judgement; risk assessment; uncertainty; social influences; social values; and sociocultural values*. Secondly, I searched PsychINFO, PubMed, Scopus, CINAHL and SSCI for articles up to and including November 2018 using the identified search terms. Articles and abstracts were screened for relevance, using the inclusion and exclusion criteria. Thirdly, I identified additional articles by using the reference and citation lists of the journal articles identified by the database searches.

## **6.4 Search Results**

My initial searches yielded 89 articles. When duplicates were removed the total comprised 77 articles. Following title and abstract screening, 50 were evaluated as full text articles. I supplemented the electronic search by scanning the reference lists of the full text articles I read. An additional 28 articles were identified. 43 full text articles then were analysed in detail and 24 were excluded. Reasons for exclusion and references to these excluded articles are presented in Appendix 24. The remaining 19 included articles comprised 16 articles based on in-depth interviews with doctors or patients, 1 based on telephone interviews, 1 based on focus group discussions and 1 systematic review. Of these 6 were conducted with doctors, 10 with patients (one of which was with women patients only) and 3 with both patients and doctors. Most of the literature identified either did not distinguish between, or did not state whether the data were based on, primary or secondary prevention. Only three included studies focused solely on primary prevention (Jansen et al., 2017, Saukko et al., 2012, Silwer et al., 2010). The types of journals from which these articles were chosen differed and can be broadly classified as ‘medical’ (n=13), ‘sociological’ (n=5) and ‘psychological’ (n=1) in nature. Characteristics of the included studies are described in Supplementary Appendix 25.

## **6.5 Main Findings**

### **6.5.1 Perceptions and Medicalisation of Preventative Health and Risk**

Unsurprisingly, the presentation of the ‘problem’ that statin use addresses differed according to the differing disciplinary orientations of the journals from which studies were selected and also the differing theoretical perspectives of the studies reviewed. In addition, there are variations in how the authors of the articles included in the review think the problem should be conceptualised. For example, (Polak, 2016a) questions ‘the usefulness of risk and uncertainty as key concepts for theoretical accounts of what is going on when people consider taking preventive medication’. A prominent and recurring theme in the medical literature on statin use is adherence to statin therapy, which is largely reported as low, and considerable variation in prescribing of statins by doctors is reported (Silwer et al., 2010). In these studies, it is taken for granted that the ‘clinical risk’ of hypercholesterolaemia requires medical intervention. ‘Non-compliance’ with or ‘non-adherence’ to statins was widely assumed by doctors who were interviewed

as a problem (Ab et al., 2009) associated with adverse health outcomes (Fung et al., 2010). In addition, this assumption frequently underpinned the justification for the study itself (Durack-Bown et al., 2003, Gialamas et al., 2011). Statin therapy is generally represented as a cost-effective (Gialamas et al., 2011) and ‘well established’ way of preventing cardiovascular events (Krüger et al., 2018).

In contrast, some of the sociological and psychological literature considered how high cholesterol had been represented and accepted as a legitimate medical problem with an associated medical solution. Polak (2016a) (emphasis my own), whose research adopts a grounded theory approach, notes that ‘from a *biomedical perspective* prevention is synonymous with risk reduction’. Drawing on the sociology of diagnosis, healthism and health promotion theories, Jovanovic (2014) discusses the ‘implications of high cholesterol being promoted as a disease factor rather than a risk factor for cardiovascular disease’, contending that high cholesterol has been *created* as a disease. Exploring how risk assessment technologies generate the clinical states they seek to represent, Saukko et al. (2012) argue that risk assessment in itself ‘generates’ high risk. Rather than a risk factor being identified first and treatment after, ‘cholesterol gained traction as a risk factor only after the development of targeted drugs.

This co-development of risk factor and drugs has continued ‘... as the category of high cholesterol has expanded to encompass increasingly lower levels of cholesterol’ (Saukko et al., 2012). Thus, risk assessments and clinical guidelines ‘configure patients at high risk’. In addition, Saukko et al. (2012) contend that because target levels of cholesterol are difficult to achieve using lifestyle changes only, this ‘creates a contradiction between the moral public health agenda endorsing the benefits of behaviour change and the precise biomedical targets, which frequently can be achieved only with drugs’. A systematic review that synthesised studies about patients attitudes and beliefs about taking statins described how the use of statins can lead to the ‘medicalisation of the population’ (Ju et al., 2018). Some of the themes identified in this review included patients questioning the utility of statins, being affected by side effects from statins and being sceptical about overprescribing statins and feeling pressure from doctors to begin statin therapy. However, the identification of these themes was to inform methods of increasing adherence to statins. In their conclusions the authors recommend, for example,

‘pragmatic ways to support medication taking’, which ‘may help patients feel more in control in their decisions regarding medications for CVD prevention’ (Ju et al., 2018). Thus, little attention was paid to the broad adverse effects of medicalisation on society or on individual patients.

Within the studies I reviewed there was remarkable concurrence from the participants that high cholesterol requires medical intervention. Polak (2016a) found that patients reified ‘cholesterol’ as a current problem rather than a future risk. In this context, patients reported that ‘prevention is a good thing, a sensible objective’ (Polak, 2016a) and that statins were a necessary, valid and important treatment for high cholesterol (Kirkegaard et al., 2013, Tolmie et al., 2003). Some patients described the risk of high cholesterol as akin to ‘Russian roulette’ and ‘drunk driving’ (Durack-Bown et al., 2003). Even ‘non-adhering’ patients reported that it is ‘unsafe to have high cholesterol levels’ (Fung et al., 2010). Some doctors accepted that the recommendations of clinical guidelines were relevant to all patients (Jansen et al., 2017), while others questioned the value of statins in some (Ab et al., 2009), for example, in old or frail patients, terminally ill patients, multimorbid patients and those who were close to their cholesterol targets (Jansen et al., 2017).

### **6.5.2 The Perception, Negotiation and Construction of Candidacy for Statin Therapy**

Prescribers of statins may consider their recommendations as synonymous with risk reduction (Polak, 2016a) and their beliefs about risk, statin effectiveness and ability to prolong life are significantly associated with their willingness to initiate treatment (Bonner et al., 2015). Hypercholesterolaemia has been described as a ‘virtual disease’ (Durack-Bown et al., 2003) because most people who take statins for the primary prevention of CVD do not experience symptoms. Therefore, the patient’s perceived susceptibility to future health problems, perceived severity of that future problem and perceived benefit of the treatment must all outweigh any possible potential adverse effect of the medicine (Ju et al., 2018). People are more likely to accept and adhere to treatment if they think that their risk of future disease is high (Bonner et al., 2015). However, as one study found, ‘the concepts of “need” and “choice” were often implicitly presented as mutually exclusive’ (Polak, 2016a) and some patients regard taking statins as

‘somewhere between essential and critical’ to minimise ‘catastrophic CVD’ (Ju et al., 2018). One study reported how *all* the patients interviewed said they needed statins (Gialamas et al., 2011).

As noted, in the studies conducted from the biomedical perspective, the negotiation of candidacy for statins was phrased in terms of compliance or adherence. In this context doctors and patients reported reasons for non-compliance by patients. These included side effects (Ab et al., 2009, Bonner et al., 2015, Jansen et al., 2017, Durack-Bown et al., 2003, Turner and Shaw, 2013, Nixon and Kousgaard, 2016, Fung et al., 2010), not having enough knowledge (Ab et al., 2009), being averse to taking medicines in general (Bonner et al., 2015), patients feeling that they are too young to take statins (Bonner et al., 2015), the absence of symptoms (Tolmie et al., 2003), preferring to reduce CVD risk by lifestyle changes (Fung et al., 2010), not wanting to be associated with being ill (Will and Weiner, 2013), and scepticism about the benefits of statins (Tolmie et al., 2003).

In addition, non-compliant patients reported not being sure of the importance of statins and that they were inconvenient to take (Fung et al., 2010). This was confirmed by some doctors who said that patients have ‘a poor understanding of the concept of cardiovascular risk factors’ because risk is ‘unpredictable and abstract’ (Durack-Bown et al., 2003). Some patients may feel pressure from doctors to begin statin therapy and reported ‘giving in’ after the doctor ‘persuaded’ and ‘threatened’ them with the possibility of future CVD complications (Ju et al., 2018), however, patients usually accepted the doctor’s view (Will and Weiner, 2013). In addition, the decision to take statins may depend on how patients value other priorities over the perceived benefits. One systematic review of patients’ beliefs and attitudes to taking statins reported that patients with other co-morbidities such as diabetes prioritised other medications over statins, while some older people perceived being able to live without the ‘hassle’ of taking statins as more important than lowering cholesterol (Ju et al., 2018).

Thus, lay peoples’ judgements of medicine use are often presented in the literature as rational, whereby they perform an evaluation about the benefits and harms of medicine (Will and Weiner, 2013). However, Saukko et al. (2012) contend that ‘the estimate of CHD risk is not a natural fact but focuses attention on very specific aspects of reality,

such as cholesterol, and articulate socially negotiated thresholds for high risk'. Citing Rosenberg (2007), they describe how people who are defined as being at high risk end up with 'proto-disease'. Rather than focusing solely on patients' cognition, researchers should also consider how these conditions are 'being created in specific ways by the risk assessment framework, which encompasses technologies, public policies, clinical guidelines and practice as well as industry operations (Saukko et al., 2012).

Kirkegaard et al. (2013), using an ethnographic approach, describes how information about risk and high cholesterol is 'reinterpreted in everyday social life' (Kirkegaard et al., 2013), whereby knowledge and norms are only two of several premises for action. The apparent contradictions between people's knowledge about a given matter and their behaviour can be explained by how people 'navigate between different concerns to overcome the discrepancy between knowledge about the right thing to do according to advice from health authorities (including the GP) and social relations that may imply risky behaviour' (Kirkegaard et al., 2013). Knowledge is a social practice derived from multiple sources including everyday life as well as from 'medical/moral instructions' (Kirkegaard et al., 2013).

Highlighting how processes of medicalisation can be gendered, Jovanovic (2014) describes the creation of the disease of high cholesterol as a dominant idea that is particularly salient for women. She contends that there is a 'trifecta' of high cholesterol promotion linked to functional food advertising; health promotion literature; and cholesterol-lowering medication. Women have been 'bombarded with messages that 'encourage self-scrutinization and an individualized focus as both cause and solution for this new disease' (Jovanovic, 2014, p.120). The women in this study were found to accept this disease framing that now dominates the public sphere.

### **6.5.3 Assumptions about Risk, High Cholesterol and Statins**

A key assumption in much of the literature is that patients use information about risk to make decisions about their health and drug consumption (Polak, 2016a). However, for many patients, the link between the risk factors and disease may not be appreciated (Durack-Bown et al., 2003) and a person cannot ascertain themselves, without medical tests, whether or not there has been an improvement. Instead of giving credence to

complex explanations of risk reduction, it has been suggested that patients are motivated to take statins depending on the circumstances under which statins are prescribed, the confidence and trust they have in their prescriber (Silwer et al., 2010), how much that prescriber emphasised the need for therapy (Tolmie et al., 2003), and how that advice is regarded as applying to them personally (Polak and Green, 2015). In addition, rather than being seen as one of several risk factors that *may* contribute to heart disease, patients may reify and evaluate high cholesterol as a current problem (Polak, 2016a). However, one study found that some doctors emphasise the need to clarify that hypercholesterolaemia, *per se*, is not a disease (Durack-Bown et al., 2003). Conversely, some of those who refuse statins have explained their decision in terms of the ‘inherent uncertainty of information about the future’ (Polak, 2016a). Some patients who discontinue statins reported uncertainty about the efficacy of statins due to the absence of visible improvements in their health conditions and expected to ‘feel nothing’ on cessation of statins (Ju et al., 2018).

Some studies report that doctors tend to explain patient non-compliance in terms of the patient not having enough knowledge (Ab et al., 2009). However, patients’ knowledge comes from a number of sources, not just the doctor, including the experience of family and friends, lay sources, the internet (Fung et al., 2010). Those who are receptive to taking statins have had this attitude reinforced by family, friends and the media (Bonner et al., 2015). The negative impact of media on attitudes to statins has been cited by some doctors as a reason for non-adherence (Krüger et al., 2018). In addition, the information relayed by doctors to patients may not be uniform. For example, Durack-Bown et al. (2003) found that a doctor’s explanation of ‘good’ and ‘bad’ cholesterol, or ‘forbidden foods’ was influenced by the doctor’s own scientific beliefs.

While current clinical guidelines for CVD prevention recommend absolute risk (AR) assessment to guide the use of statins, Bonner et al. (2015) found that many doctors do not prescribe on the basis of AR but rather on the basis of elevated single risk factors, such as cholesterol levels. The difference between relative and absolute risk reduction, however, is complex, including for medical professionals who may be uncomfortable using numerical representations of risk reduction. In addition, this difference between absolute and relative risk reduction and abstruse explanations about cholesterol and CVD

risk may not be an effective way of understanding CVD risk or be sufficient for motivating behavioural change. Some doctors may be confused by conflicting clinical guidelines, risk assessment and feel unsure of who should be prescribed statins and why (Kedward and Dakin, 2003, Silwer et al., 2010, Ab et al., 2009). One study reported that most GPs thought that statins had little relevance for primary prevention of CVD and questioned guidelines for low-risk people (Krüger et al., 2018).

While some people prefer to use diet to reduce cholesterol, this cornerstone of prevention may be limited in practice. Many physicians and patients appreciate the difficulty of making long-term changes to one's lifestyle (Durack-Bown et al., 2003) and the relatively limited impact dietary modification has for those with higher cholesterol levels. GPs' beliefs about the efficacy of lifestyle changes influenced their method of CVD risk management (Bonner et al., 2015). If there is a generalised belief by both GPs and patients that lifestyle changes are not effective in reducing cholesterol levels, or that patients are unlikely to adhere to such changes, statin use may be legitimised.

#### **6.5.4 Socio-Demographic and Cultural Differences**

Despite the significance of socially and culturally specific disease regimes (Klawiter, 2004), few studies considered the socio-demographic or cultural differences in how people perceived or negotiated statin candidacy. Krüger et al. (2018) reported low adherence to statin therapy in older patients and those with lower educational levels. However, those with high levels of education were described as 'particularly challenging' because they were sceptical about medications and the evidence from trials, as well as the expertise of the GPs (Krüger et al., 2018). Doctors reported that this group were 'excessively' concerned about developing muscle symptoms, which can be a side effect of statins (Krüger et al., 2018). Fung et al. (2010) conducted an analysis for non-adherence to statins and found that no patient cited out-of-pocket drug costs as a reason for discontinuing. However, this group did have health insurance and co-payments for statins were reported as generally low, so it is likely that cost was not an issue anyway. Saukko et al. (2012) assigned the patients they interviewed to one of four 'paths' in terms of how they dealt with CVD risk. These were the pharmaceutical path, the mixed path (pharmaceuticals and lifestyle changes), the behavioural path, and the lost path. The latter comprised people who had not engaged with either medications or lifestyle methods of

reducing CVD risk and these people often fell into low socio-economic status groups or had difficult life circumstances.

Jovanovic (2014) discusses the impact of the framing of CVD risk-as-disease and contends that this is problematic, particularly for less privileged women. She argues that this ‘hypercholesterolized state of women’s health’ is structured around class lines (Jovanovic, 2014). Health promotion campaigns and policies are centred on individualised solutions and framed as the management of choice. Women, therefore, ‘can choose to be informed and women can choose to seek additional medical advice’ and by not making ‘proactive preventative choices, women are choosing by default, to be ill’ (Jovanovic, 2014). She describes this as ‘false empowerment’ whereby poverty and income inequality are ignored and social, political and economic constraints faced by poorer women are minimised.

The aim of this chapter is to examine statins particularly in the context of primary prevention. However, only three papers reported that they focused solely on this group. Two comprised analyses of doctor’s views and decision making process (Jansen et al., 2017, Silwer et al., 2010) and one of these referred only to patients over 75 years of age (Jansen et al., 2017). Both of these reported contradictory findings. Doctors either thought that guidelines were relevant to *all* patients or tailored guidelines to the individual. Doctors either were convinced that a predictable risk could be calculated for an individual, or were not. They either relied firmly on the protective mechanisms of medication or lifestyle changes, or they strongly questioned these. A third paper reported on patients’ experiences (Saukko et al., 2012). However, this study focused on patients with a family history of coronary heart disease, whose own risk had been assessed as high. Thus, their views may not represent lower risk patients with no family history of CVD.

## **6.6 Discussion**

The aim of this chapter was to provide an overview of the qualitative research literature on patients’ and doctors’ perceptions and reported behaviours in regard to statin therapy, particularly in primary prevention of CVD. The review was guided by four specific research questions. Firstly, I examined how preventative health and risk are perceived

and medicalised in the context of CVD prevention, and secondly, how candidacy for statin therapy is perceived, negotiated and socially constituted. Thirdly, I examined the assumptions about risk, high cholesterol and statins that patients and their doctors use to base ‘candidacy’ for statin therapy. Finally, I considered whether there is evidence of socio-demographic or cultural differences in these perceptions and negotiations of statin candidacy.

As noted, the process of medicalisation requires the acceptance that an issue is a legitimate medical problem, requiring a medical solution. In the literature reviewed ‘high cholesterol’ was reified as a current disease and risk had acquired ‘facticity’, that is, the status of an adverse event in its own right (Heyman et al., 2012). Thus the problemisation of high cholesterol seems to have been largely achieved. Within the medical literature most doctors and patients were immersed in this ideology and described taking statins as a good, sensible and necessary solution to the problem, thus creating ‘a single story with a lock and key problem/solution structure’ (Parry, 2003). The risks posed by high cholesterol are treated as if they are ‘material phenomena which can be directly observed and measured’ (Heyman et al., 2012), risk assessment ‘has become a potent legitimising tool’ (Brown, 2014), thus sanctioning statin use.

In otherwise healthy people, the need for statin therapy must be jointly negotiated and accepted by both patient and doctor to establish a person’s ‘candidacy’ for treatment (Annandale et al., 2007). In this context, Heyman et al. (2013) point out that while the probability of a particular outcome cannot be accurately foretold at the individual level, individuals may accept the objectivity of measures such as CVD risk assessments. However, if ‘need’ and ‘choice’ about taking statins are considered mutually exclusive by the patient, as suggested by the literature I reviewed, candidacy is easily established, and little negotiation takes place.

While ‘knowing your numbers’ and ‘treating to target’ have been described as characteristics of contemporary medicine (Moynihan, 2011), Polak and Green (2015) reported that there was little evidence that ‘understanding probabilistic risk information was ... necessary ... for making decisions about statin use’. In contrast to the idea of a rational actor who weighs up the benefits and harms of statin treatment and decides upon

the most logical course of action, the acceptance, or not, of candidacy for statins may be *socially* negotiated. The knowledge upon which patients make choices may come from many sources including family, friends, the media, as well as the medical professions. However, in contemporary life, people, and women in particular, are bombarded with messages about lowering cholesterol, and feel that they have an ‘obligation to act now to prevent future illness’ (Jovanovic, 2014). ‘Non-compliant’ patients were characterised by doctors as those who did not have enough ‘knowledge’ about the obvious risks of high cholesterol and benefits of statin treatment.

Although clinical guidelines emphasise that statins should be prescribed on the basis of a person’s overall risk of CVD, this recommendation may, in reality, have little impact on professional or lay behaviour (Prior et al., 2014). As reported above, GPs may instead focus on very specific aspects of CVD risk, namely, cholesterol levels and thresholds as a reason to prescribe statins rather than the overall baseline risk of the person as recommended by clinical guidelines (Bonner et al., 2015). This finding has been corroborated by other research (Johansen et al., 2014, Selmer et al., 2009, Byrne et al., 2018, Finnikin et al., 2017) and may be a key driver of the medicalisation process in this context. Thus, a well person becomes a person ‘at risk of illness’ by both she and her doctor accepting ‘a pre-disease (at risk) status’ (Jutel and Nettleton, 2011). Farrimond et al. (2010) describes how ‘at risk’ people may ‘occupy a liminal identity between the “healthy” and the “ill”’. This state may justify the prescription by the doctor and acceptance by the patient of a cholesterol-lowering statin.

Saukko et al. (2012) argue that assessing risk in itself *generates* high risk and also contends that risk factors and drugs, in the case of statins, were co-developed. Cholesterol, they contend, only gained traction as a risk factor after the development of targeted drugs. In other words, simply having a drug to treat a condition can stabilise the notion of the disease itself (Pollock and Jones, 2015, Jovanovic, 2014), in some cases the drug may become central to the definition of disease categories (Greene, 2007), thus forming part of the knowledge on the basis of which patients, and doctors, make decisions.

In terms of the socio-economic or cultural differences around statins use, there was very little reported. While low socio-economic status individuals were reported as less likely to commence or adhere to statin therapy, those with higher educational status caused problems for the doctors by questioning their advice, the evidence to support statin use and being over-concerned about side effects. This finding is in contrast with those of Berglund et al. (2013) who reported that highly educated people have fewer concerns about medication than those with less formal education and Heyman et al. (2012) have hypothesised that ‘faith in prevailing risk delineations correlates with height of position in societal hierarchies’. Others have reported that those with more years of formal education are more likely to ‘know their numbers’ (Moynihan, 2011) and to quantify their body (Lupton, 2013). These contradictory findings would warrant further consideration as they may indicate that the social construction of disease may differ among differing socio-economic groups.

More broadly, within this construction of disease, the responsibility for problems was reported as falling upon the individual, ignoring the social and political determinants of health. This neoliberal responsibilising and framing is often presented under the guise of ‘empowerment’ of the individual (Jutel and Nettleton, 2011). This reductionist view has been one of the earliest criticisms of the medicalisation process. Noting that it was ‘easier to put up a clinic than to pull down a slum’, Wootton (1959, cited in Davis, 2006) identified one of the key arguments against medicalisation, that by focusing on the individual one ignores the social, cultural, psychological and environmental contexts of health and illness (Clark, 2014b). The complexity, relativity and experiences of health are excluded and both causes and solutions of problems are sought in biology rather than in the social or political realms.

As I have noted, most studies, did not distinguish between primary and secondary prevention of CVD, and only three focused solely on primary prevention, two on doctors’ views and decision making and one on the experiences of high risk patients with a family history of CHD. This represents a clear research gap, given that the majority of statin users fall into the primary prevention category and that many of these would have a low risk of CVD. It is difficult to interpret how doctors’ or patients’ attitudes would vary according to the risk profile of the individual patient. Because statins for primary

prevention inhabit an uncertain and negotiated space of asymptomatic people taking a medicine to prevent a theoretical health risk, it is possible that the views and behaviours reported in the more general literature do not represent theirs.

Earlier I outlined how almost three quarters of female statin users fell into the primary prevention category compared to just over half of male statin users (Byrne et al., 2018) and Jovanovic (2014) contends that the idea of high cholesterol as disease is particularly focused on women. Thus it may be salient to consider how medicalisation in this context might be a gendered process. Women are more likely than men to be medicated and to be the ‘main targets’ of medicalisation according to Riessman (1983). This may be because the initial sites of medicalisation were those that concerned women’s bodies, for example, in the area of childbirth. The normal biological functions of a woman, menstruation, reproduction, lactation and menopause, have been pathologised and come under the medical gaze and medical meanings have been constructed for these everyday events. In addition, women live longer than men and suffer more chronic disease and so are more likely to have more opportunity to engage with medical services (Nettleton, 1996).

Feminist writers such as Riessman point out that women’s subordination to men in society as a whole may make them more vulnerable to the expansion of the medical realm, partly because the social relationship between a woman and her doctor can replicate the patriarchal structure of society in general (Riessman, 1983, Garry, 2001). The high prevalence of statin prescribing for primary prevention in women, despite their generally lower cardiovascular risk, may relate to women being more compliant with a doctor’s interpretation of events and more compliant with their recommendations because of this. Conversely, some studies have found women to be less likely to adhere to statin therapy than men (Chan et al., 2010). Any analysis of this contradiction would need to acknowledge ‘the complexity of intersectionality’, that is, that ‘relationships among multiple dimensions and modalities of social relations and subject formation’ are central categories of analysis (McCall, 2008). This issue, the broader question of the agency of women, and the influence of the gender of the doctor, are beyond the scope of this review.

Decisions to take or prescribe a medicine involve a trade-off between the perceived benefits and harms of that medicine for the individual. This trade-off is particularly salient for low-risk people choosing to take a statin for primary prevention of CVD as the patient often feels healthy and may perceive the medicine as unnecessary, with uncertain benefits and potential side effects. Conversely, it may be the case that clinicians and patients would desire a reduction in CVD, regardless of how small, if they can tolerate statins. Studies based exclusively on representative groups of people in the primary prevention categories are needed to elucidate this point.

## **6.7 Conclusion**

There is little doubt that preventative medicine in the field of CVD has been a site of medicalisation, with large increases in the number of people taking statins over the last decades. The ‘lower the better’ message for cholesterol levels is reinforced by health promotion and media and has become ‘the received wisdom’ embedded into ‘what everyone knows’ (Hann and Peckham, 2010). Central to this process has been the heuristic that identifies elevated cholesterol as a medical problem in its own right warranting statin treatment, as well as the difficulties encountered by doctors and patients in understanding, interpreting and communicating risk. While my aim was to review the literature pertaining to statins for the primary prevention of CVD, I found that there has been very little work focusing specifically on primary prevention, or on women. Given the large proportion of people in general, and women in particular, taking statins for primary prevention, these areas warrant further considerable exploration.

# **7 Statins for the Primary Prevention of Cardiovascular Disease: A Qualitative Exploration of Irish Prescribing and Usage Trends in the Context of Medicalisation and Governmentality**

## **7.1 Introduction**

To date, much of the analysis of the processes of medicalisation in the qualitative literature has drawn on Foucauldian theories of power, particularly the concept of ‘governmentality’. Governmentality refers to a system of power that regulates society through the adoption of belief systems shaped by political and social norms. In the context of medicine, prevailing understandings of the nature of disease facilitate the creation of hegemonic disease regimes that are not static, but rather are ‘culturally, spatially and historically specific’ (Klawiter, 2004). In this way, a dominant ‘regime of truth’ of a particular time (Wilson and Prior, 2017) is created and a particular medical vocabulary and ideology are used to order and define the problem (Halfmann, 2011). ‘Governing’, therefore, does not require a coercive or authoritarian sovereign power and incapsulates both the governing of oneself as well as the governing of others (Lemke, 2002). Foucault used the French term ‘conduire des conduites’, generally translated as the ‘conduct of conduct’, to describe this key phenomenon of governmentality:

Perhaps the equivocal nature of the term conduct is one of the best aids for coming to terms with the specificity of power relations. For to ‘conduct’ is at the same time to ‘lead’ others (according to mechanisms of coercion which are, to varying degrees, strict) and a way of behaving within a more or less open field of possibilities (Foucault, 1982).

If, in the context of medicine, dominant ‘regimes of truth’ emerge that are specific to particular times, then arguably the prevailing authoritative discourse in contemporary medical regimes is preventative health and the management of risk. The modern medical encounter increasingly involves ‘nudging’ ... in subtle ways that do not affect ... freedom of choice’ (Wilson and Prior, 2017), rather it:

... provides guidelines about how patients should understand, regulate and experience their bodies... (through) ... comparison of individuals against an established norm ... It is exercised not primarily through direct coercion ... but rather through persuading its subjects that certain ways of behaving and thinking are appropriate for them (Lupton, 1997b).

However, where there is power, there is resistance (Foucault, 1998), described by Foucault as 'counter-conduct', involving 'the transgression and contestation of societal norms' (Death, 2010). Interestingly, it has been argued that when conduct is regulated by a regime of scientific veridiction, it is subordinated to 'the pre-eminence of this regime' and 'counter-conduct becomes inconceivable ... nothing more than a form of irrationality' (Davidson, 2011).

As my research took place in the Irish context, I was interested in identifying and explaining aspects of the cardiovascular disease (CVD) regime that may be specific to Ireland. Certainly, the use of statins was adopted enthusiastically in Ireland; in a study of twelve European countries between 1997 and 2003, the largest increase in the use of statins was found to be in Ireland (Walley et al., 2005). It has been argued that health policy in Ireland exhibits key characteristics of neo-liberal governmentality by repositioning power away from a centralist State to 'government as a series of agencies, institutions and actors through which power becomes manifest' and risk prevention by the individual is strongly promoted (Edwards and Fernández, 2017). Doctors are delegated 'power and responsibility for population health' and strategic health policies are part of the 'discourse coalition' (Wilson and Prior, 2017).

Edwards and Fernandez (2017) have argued that governing and medicalising occur in response to two forces, that of the disciplining medical encounter itself and that of the regulatory nature of public health initiatives. Strategic health policies are 'heavily politicised blueprints' of health which identify areas of health requiring governance (Wilson and Prior, 2017) i.e. they are technologies of government (Edwards and Fernández, 2017). In 1998 the Minister for Health and Children in Ireland established the Cardiovascular Health Strategy Group, which published the *Building Healthier*

*Hearts – Report of the Cardiovascular Health Strategy*. This report did not recommend risk assessment for the entire population but rather a combination of ‘opportunistic and systematic risk assessment, with a very structured approach to the management of those identified as being at high risk’ (Department of Health & Children, 1999). However, a new National Cardiovascular Health Policy (2010–2019) was published in 2010 suggesting a shift in emphasis from those at high risk of CVD to a whole population approach, noting that:

Effective prevention requires a shift of the entire distribution of a risk factor (e.g. raised cholesterol) to lower values. It should extend beyond a focus on high-risk individuals, utilising cholesterol-lowering therapies, to population-based approaches, preventing the development of the risk factors themselves (Department of Health & Children, 2010).

The change in emphasise between these two Irish policy documents exemplifies one aspect of the process of medicalisation whereby the definition of disease is widened, thereby significantly increasing the proportion of the population who could be eligible for medical intervention (Moynihan et al., 2013).

Informed by the concepts of governmentality and medicalisation, this chapter aims to examine the ‘type of assumptions, of familiar notions, of established, unexamined ways of thinking, the accepted practices’ (Foucault, 1994 [1981]) on which the ‘disease regime’ of CVD prevention in Ireland is based. I call this the ‘Irish CVD regime’. I was interested in exploring if statin use was indicative of ‘conformity with broadly recognized biomedical identities’ (Halfmann, 2011) informed by purportedly ‘objective and rigorous scientific knowledge’ (Lupton, 2012). In Section 7.2 I briefly describe the relevant literature, study design, participants and the methodological and analytic approach used. In Section 7.3 I discuss the results from the interviews I conducted and their implications in the context of existing literature, while in Section 7.4 I present the conclusions to the chapter.

## **7.2 Methods**

### **7.2.1 Literature Review**

Prior to undertaking this analysis, a literature review was conducted to aid development of key questions and topics – see Chapter 6. I found that much of this literature rests on the assumption that being deemed at risk of CVD is an adverse event in its own right, that prescribing statins is appropriate and that adherence to statins a worthy goal. It is worth noting that medicalisation is a process that occurs at multiple levels, the conceptual level whereby ‘a medical vocabulary’ is used to ‘order or define the problem at hand’; the level of doctor-patient interaction; and, at the institutional level whereby organisations ‘adopt a medical definition and approach to a problem’ (Halfmann, 2011). Thus, I opted for a Foucauldian mode of analysis that emphasises the significance of problematisation and aimed to recruit patients and doctors, as well as those actors who might influence the institutional acceptance of statin use. I approached the semi-structured interviews that I conducted as spaces where people reveal if and how they and their beliefs fit into the prevailing ‘regimes of truth’ (Bonham and Bacchi, 2017).

### **7.2.2 Study Design and Participants**

I followed COREQ guidelines on the design and reporting of qualitative research (Tong et al., 2007). Firstly, GPs were invited to participate through email invitations sent to members of the Western Research and Education Network (WestREN), which is a research partnership between more than 185 GPs and general practices and the Discipline of General Practice at the National University of Ireland, Galway. Secondly, for patients, the Irish Countrywomen’s Association (ICA) and the Irish Prison Service (IPS) were asked to invite members to participate by email. These organisations were targeted to ensure a broad representation of potential participants likely to be prescribing or taking statins for primary preventions. The ICA has a membership of widely dispersed, largely rural dwelling women. The IPS was approached for pragmatic reasons of access, being a large employer of a cross-section of Irish adults. Both organisations were approached also because of personal contacts within them, which enabled access to ‘gate-keepers’. Patient participants were considered for inclusion in the study if they were over 50, had been prescribed statins by their GPs for the primary prevention of CVD and had taken, declined or discontinued these statins. Thirdly, ‘opinion leaders’ were identified through stakeholder mapping and contacted directly. Although I aimed to recruit actors who were

involved in guideline development, only one such interviewee came forward. However, I believe that the diverse backgrounds of these clinical opinion leaders enriched the study.

There were 20 research participants, consisting of eight members of the public, seven GPs and five opinion leaders – see Table 7.1. The members of the public comprised three women and five men between 50 and 80 years of age all of whom had been prescribed statins for primary prevention. The GPs comprised two women and five men between 30 and 70 years of age whose practices were located in rural and urban areas. The clinical opinion leaders were in senior health service, policy or research related positions comprised one woman and four men ranging in age from 50 to 70 years.

Table 7-1: Characteristics of Participants

Type of participant	Number of participants	Age					Gender		Rural/Urban	
		30-40	40-50	50-60	60-70	70+	F	M	Rural	Urban
GP	7	1	2	2	2	0	2	5	3	4
Member of the public	8	0	0	6	2	0	3	5	7	1
Opinion leader	5	0	0	4	1	0	1	4	1	4

Semi-structured interviews were conducted between April and June 2017, at locations convenient to the participants, each with a single session of between half an hour and one hour. Ethical approval was granted by the Research Ethics Committee of National University of Ireland, Galway (Reference number 16-Oct-03). All participants consented in writing to take part in the interviews, which were audio-recorded. There was potential for self-selection bias (Robinson, 2014), particularly in the GPs, whereby those who volunteered to be interviewed may have been those with a stronger interest in the topic. Men were over-represented in all groups; six women were interviewed compared to fourteen men. All participants were of Irish origin, apart from one medical consultant who was Middle-Eastern, but who had lived in Ireland for some time.

### 7.2.3 Data Analysis

A Foucauldian-inspired post-structural analytical strategy was used to analyse the interview transcripts. This comprised a method of analysis developed by Carol Bacchi, called ‘What’s the Problem Represented to Be?’ (WPR). The starting point of WPR is

that ‘that which we propose to do about something indicates what we think needs to change and hence what we think the problem is’ (Bacchi and Goodwin, 2016). The analysis used a series of questions posed to identify how problems are thought about and acted upon by the interviewees. This method:

contrasts ... (with) the ways in which ‘problems’ are commonly conceptualized in health policy analyses ... The starting point is a close analysis of items that are ‘successful’, in the sense that they make the political agenda, to see how representations of the ‘problems’ within selected policies limit what is talked about as possible or desirable, or as impossible or undesirable. This form of analysis thus enables critical reflections on the substantive content of policy initiatives in health policy (Bacchi, 2016).

A broad interpretation of ‘governing’ is facilitated by Bacchi’s method, as governing extends ‘well beyond political institutions ... to encompass the full range of knowledges or discourses and sites involved in societal administration. Because the practices and theories of ‘experts’, researchers and professionals from diverse fields ... are involved in governing, they become targets for critical analysis’ (Bacchi, 2016).

My analysis began by firstly asking: if statins are the solution, what is the problem? Secondly, what presuppositions and assumptions underlay these representations of the problem? Thirdly, how were the prevailing governing knowledges created, particularly those relied upon by experts such as GPs, consultants and researchers. This includes consideration of influential discourses disseminated through professional publications, guidelines and training. Fourthly, I was alert to any views or reported behaviours that dissented from the prevailing discourse among the interviewees. Finally, I considered how the representations of the problem ‘direct or constrain thinking or action, create those who are able to speak authoritatively on the subject and explore power relations and the technologies of governing and self-governing’ (Lawless et al., 2014). This type of analysis does not amount to ‘putting into question the *reality*’ of cardiovascular disease, rather, it argues that cardiovascular disease and the policy of prescribing statins are products of a particular way of both thinking about cardiovascular disease and ‘enacting the practice of governing’ in its prevention (Bletsas, 2012). All interviews were

recorded and transcribed verbatim. The first stage of analysis consisted of listening, reading and re-reading the interviews to enhance familiarisation (Green et al., 2007) and facilitate ‘thinking through the analytic process’ (Lawless, 2010). Bacchi’s WPR questions were used to interrogate each interview transcript and data were examined, sorted and coded accordingly. A third stage of analysis was then undertaken, whereby the coding from all interviews was aggregated into themes based on the WPR questions.

## **7.3 Results and Discussion**

### **7.3.1 Problematisation, Underlying Conceptual Logics and Resistance**

The representation of the problem for which statins are a solution was remarkably consistent in the interviews. In concurrence with a recent UK study (Polak, 2016a), rather than high cholesterol being seen as one of several risk factors that *may* contribute to heart disease, it tended to be reified and evaluated as a current problem, an adverse event in its own right (Heyman et al., 2012):

There is a history of cholesterol in my family, not so much a history of heart disease ... it was a complete shock to me that I might have cholesterol problems (PA, female 70-80).

Despite the lack of symptoms and the un-embodied nature of their ‘illness’, participants were generally very aware of the numerical details of their current cholesterol levels and some discussed changes in these levels in great depth.

Originally it was about 6.1 and I got it down to 4.2 so normally it is around the low 4s. It is still a little bit high (CD, male 50-60).

This ‘knowing your numbers’ has been described as a key characteristic of modern medicine (Moynihan, 2011) and is underpinned by evidence-based medicine, described by Bacchi (2012) as the broad ‘problem-solving motif currently dominating the intellectual and policy landscape of western industrialized societies’. Angus et al. (2005) describe how many people accept the reality of a risk factor such as elevated cholesterol by relying on the ‘interpretive powers of medical hermeneutics’ to establish their candidacy for statins. This ‘leap of faith’ in the ‘capacity of health sciences to penetrate

the surfaces of the body and visualize its mysterious interior' is a source of medical power (Angus et al., 2005). Those I interviewed overwhelmingly said they considered the recommendations for use of statins as evidence-based and scientific. However, considerable ambivalence was evident; while most GPs and patients adhered to the CVD regime, 'and you can't argue with the figures' (CS, male GP 50-60), a certain uneasiness remained. For example, one GP attempted to separate 'the scientist part of me' from 'the emotional side of me', explaining 'I am not a full believer in them, I am not 100% ... they have to have the evidence and all that ... but ... I don't trust it fully' (DS, female GP 40-50). Another GP, described a distinct bifurcation between the 'science' that underpins medical practice, which *should* be adhered to, and the daily reality of practice:

Where do you draw the line really? ... The science says 'yes' ... There is a pill for everything and at some point, you have to take the holistic approach, as in, that is the science and that is the person (SC, male GP, 50-60).

Similarly, several patients expressed ambivalence; for example, one man fluctuated between frequently stating his scepticism about statins while noting that his cholesterol was '6.1, it is too high, it is risky' (CD, male 50-60). This patient duly took statins daily and stated 'I'd prefer not to be on them obviously, but that's the way it is'. Thus, the idea of needing statins and choice were presented by most as mutually exclusive, concurring with a Scottish study (Tolmie et al., 2003). The patients I interviewed, despite a commonly expressed degree of ambivalence, have been persuaded 'that certain ways of behaving and thinking are appropriate for them' (Lupton, 1997b), and that taking statins is a normal (Polak, 2016b) even 'desirable aspect of healthy living' (Greene, 2007). One man, with a family history of Alzheimer's disease, was conflicted because he thought that statins have been implicated in the development of dementia (Food & Drug Administration, 2012). He stated that he would prefer to die of a heart attack, which he saw as a possible consequence of not taking statins, than develop Alzheimer's, which he saw as a possible consequence of taking statins. Despite this dilemma, the man remained on statins. This 'bracketing-out' of uncertainty has been described as intrinsic to the personal relationship between a patient and a professional he/she trusts (Brown et al., 2015).

Two patients refused statins, warranting some consideration as the sample size is small and their attitude and behaviour may be representative of many of those who are prescribed statins. Indeed, adherence to statins is generally reported as low as 50% (Lemstra et al., 2012). One woman, who did not express very strong opinions, had discontinued statins against the wishes of her GP and did not seem to be unduly worried about high cholesterol. Although asked, she could not explain this apparent indifference, apart from the fact that she had once attended a talk by a consultant totally opposed to the use of statins, and she could not remember exactly why she had remained off statins. This may be indicative of what Lupton (1997b) describes as the ‘diversity of responses to the strategies of medical power and the contradictions and conflicts that exist in the ways people respond to doctors’. Lupton described a study of Scottish mothers receiving home visits from health visitors who responded in various ways to attempts to shape their behaviour ‘including direct rejection and attack on the value of the health worker’s attention, non-cooperation, silence, escape, avoidance and most commonly of all, concealment’ (Bloor and McIntosh, 1990). Demetriou (2016) has argued that counter-conduct is not confined to conscious or articulated resistance but ‘can be a thought, a reflection, or the lack of reflection’. This woman’s refusal to take statins appears to be a passive dis-engagement with medical power rather than any expression of active resistance. In contrast, the other ‘refuser’ verbalised his resistance thus:

... the doctor ... said we have no choice to put you on statins. So, I said ‘You may have no choice, but I do, I am not going on statins.’ So, they told me ‘You realise the possibility of heart disease, stroke, heart attacks, blah, blah, blah.’ I have known from thirty years or more that I wasn’t going to live forever ... Still no statins ... Now am I doing the right thing, am I doing the wrong thing? I don’t know (CS, male 50-60).

Both these interviewees who refused statins seem to contradict Foucault’s contention that within the scientific regime of veridiction counter-conduct becomes ‘inconceivable’ (Davidson, 2011). These examples may indicate that there is a complex heterogeneous reaction to the authoritative scientific framing of the problem of high cholesterol.

Some would argue that health has come to be defined as risk reduction (Dumit, 2012). The conflation of risk and disease are central to the discourses of both patients and doctors in my study to varying extents. Risk assessments created expectations of target levels of cholesterol and provided a ‘sense of safety’ when those targets were reached (Saukko et al., 2012), which may be sufficient for scepticism to be overcome. Some patients, for example, believed that once they are taking statins they are completely protected from CVD, thus overestimating the effectiveness of the medicine. One GP said that the majority of people simply believed ‘‘take a statin, don’t have a heart attack’ and clearly that is not the case’ (RD, male GP 50-60). However, in contrast, some doctors and patients were completely convinced of the benefits of taking statins. One consultant described statins thus:

I ... look on them as drugs that are akin to vitamin supplements, almost over the counter... I think I would almost be on the fluoride in the water group of believers in statins (DS, male consultant endocrinologist, 50-60).

In my study, only one interviewee, a medical consultant, completely rejected the current conceptualisation of the link between cholesterol and CVD. His is not an isolated position, as a number of prominent commentators have disputed the link (Demasi, 2018) and it is possible that, in time, a new, albeit still biomedical, consensus will emerge.

While influenced by government health strategies, clinical guidelines and medical journals, in general the doctors I interviewed sought condensed versions of information; from continuing medical education programmes and courses, newsletters and websites of medical organisations. They depended on these documents and training opportunities, many expressing the difficulty in keeping up with recommendations and often having a favourite familiar source of information:

I can’t say I follow any guidelines very closely... it is patchy. I would read some journals ... but I don’t read them regularly or in any great depth. Occasionally, I read hospital medical stuff or cardiology stuff ... now as I get older there is so much stuff coming at you from all sides, it is very hard to keep up to date with all the recommendations (BD, male GP, 60-70).

In a comparison of Australian and Irish GPs' prescribing practices, Montgomery (2012) noted that 'peer influence on prescribing in Ireland due to the popular peer-led (Irish College of General Practice continuing medical education) meetings' is a distinguishing feature of Irish GP practice. Indeed training events exerted a strong influence on some GPs' practice:

I was at a recent GP's ... course ... they tell you all the latest studies and there are always new studies on statins ... I was at one two months ago and they were talking about (how) really, we should be pushing statins more. So, since I came back from my course I am a bit more likely to prescribe them (DC, female GP, 30-40).

However, as noted, despite the authoritative assertions of these influential documents and peer-to-peer training, and despite the fact that most GPs largely complied with their recommendations, there was a view that increasing the use of statins has come about due to a process of 'creeping medicalisation', as described by one GP. He seemed to find himself in a dilemma; the notion that 'there is a pill for every ill' seemed to chafe against the idea of 'good science', whereby one cannot 'argue with the figures' when 'science says it is of benefit'. As an older GP, he compared statin use to other popular treatments throughout his career that have now fallen out of vogue, such as HRT, and asked 'should we be even treating high cholesterol?' (CS, male GP, 50-60). A 'pendulum of treatments' (MK, male GP 60-70) was described whereby GPs may enthusiastically adopt new therapies, perhaps reduce their use due to bad press or safety scares, and finally begin again to use them at lower and, he implied, more appropriate rates. When asked at what point of the pendulum did statins currently lie, this GP replied that he thought statins in primary prevention were still overused and that the pendulum had not quite reached equilibrium. Thus, tensions do exist between GPs' own wisdom and the authority of clinical guidelines and other policy documents. GPs, for example, may feel a sense of safety by complying with the current orthodoxy, one describing 'my concern was if I didn't start her on them and that she got an event that I would be held responsible. If I started her on them and nothing happens people say, why did you put her on it?' (DC, female GP, 30-40). Some GPs admitted to diverging from current treatment thresholds in special cases:

... I have a 96-year-old lady who in the past three or four years has got dementia, her cholesterol was usually around 10 or 11 thirty years ago ... and I tried her on various drugs and she had side effects. She got to her early 70s and I said, 'you have got this far without them and you are doing well, I am not going to upset the apple cart.' She got another 25 years before she had any problems (DB, male GP 60-70).

In addition, several of the GPs and patients suggested undue influence from the pharmaceutical industry on prescribing. Montgomery's (2012) comparison of prescribing between Australian and Irish GP practices found that some Irish doctors acknowledged the importance of pharmaceutical manufacturing to local industry. A significant amount of atorvastatin, for example, is manufactured in County Cork and this was mentioned by one GP '... simvastatin was the flavour of the month for a while... and then atorvastatin...the thing with atorvastatin, it was manufactured by Pfizer' (MK, male GP, 60-70). One biostatistician who had attended a meeting of European cardiologists was explicit about the marketing attempts of the pharmaceutical industry, noting that 'the influence of drug company promotional budgets on prescribing was completely naked' (CR, biostatistician, 60-70).

### **7.3.2 Subjectification**

Bacchi describes subjectification effects as the effect of problematisation 'which define who we are, how we feel about ourselves and who is attributed responsibility for a problem' (Goodwin, 2012). In other words, the type of person we present ourselves to be is as a result of normalised rules and power/knowledge relations that produce acceptable subject positions (Bonham and Bacchi, 2017). In otherwise healthy people, the need for statin therapy must be established and accepted by both patient and doctor to establish a person's 'candidacy' for treatment (Annandale et al., 2007). The eligibility for this type of medical candidacy requires a concurrence either of beliefs of the patient and doctor, or an acceptance by the patient that the doctor's view is correct. In general, GPs and consultants described trying to engage in shared decision making but several doctors said that patients would prefer the doctor to ultimately make the decision:

... my practice would be to try and empower the patient to try and make a joint decision rather than leave it to me to say yes or no. But inevitably oftentimes it does fall down to me to say yes or no ... they want to hand over the care ... that's just the natural thing of it (CS, male GP 50-60).

Many patients said they questioned the doctor and compared themselves favourably to other people who did not question the prescription of medicines. However, while this seemed to imbue the person with a sense of 'doing the right thing', most patients, even those expressing reservations about taking statins, did not choose to go against the doctor's recommendations. It seemed that questioning was a good thing to do, of itself, and that this in some way identified them as suitably 'empowered' and absolved them from the more difficult outright refusal of a medicine recommended by a doctor:

I did not go with their opinion. I chose to give it twelve months and see how it goes and the cholesterol over that point in time had increased. (The doctor asked) ... will you consider having it (statin)...yes, I would ... when I ask his opinion, he is not a judge in court giving a decision judgement. He is adding to or taking from the information I already possess (DP, male 50-60).

On the other hand, some doctors described how they had to persuade their patients into taking statins; 'You advise them, you tell them, you coach them, you cajole them, you review them, are you taking your medicines?' (CS, male GP 50-60). This process was described by Freidson (1970) as the 'tendency of the profession, once jurisdiction over some behaviour has been secured, to begin acting as moral entrepreneurs'.

The single consultant who rejected the cholesterol theory outright described how people who were inclined to reject statins came to him because they knew his opinion, and that by consulting him, in some way were given permission to refuse the drug.

They know my views ... and they came to me because they don't want to take it... they want reinforcement for their decision not to take it...and ... they go back to the GP and the GP says 'yes, I agree' ... the GP doesn't want to carry the can, so they come to me (HB, consultant vascular surgeon 50-60).

These patients lack ‘the authority accorded to bio-medical knowledge’ (Blume, 2017) and required the authority of this consultant to legitimise their decision. This example is interesting too given the current emphasis on ‘patient preferences’ and ‘shared decision-making’ in medicine (Albarqouni et al., 2017, Barratt, 2008). In an analysis of the ‘expert patient’, Blume (2017) noted that a patient’s experience is:

treated as authoritative, as worthy of being characterized as ‘knowledge’ only to the extent that it appears compatible with medical knowledge and assumptions. A patient who sets off on a radically different road ... is likely to encounter anything but respect for the reasoning behind her decision.

Some of the patients dissociated themselves from others who were pill-takers. Eborall and Will (2011) described this clash between a general dislike of taking pills and concern about the moral implication of being seen as a ‘pill popper’, which conflicted with the ‘shared belief about preventing cardiovascular disease’. One explanation for how people legitimised this position was that participants in my study seemed to believe that statins were a fail-safe way of preventing CVD. The patients who had refused statins also differentiated themselves from people who took lots of medicines. One woman described friends who were taking a lot of medicines and wondered ‘Are you just rattling around on pills?’ However, statins were represented by many of the interviewees as a *different* kind of medicine to those that people would not take. They were justified as ‘necessary’ and therefore did not tip the person over into being a ‘medication man’ (or woman). This man, who was taking statins, stated:

I do not take drugs ... For me, being on tablets of any description is an inconvenience and unless I am convinced it is absolutely necessary I won’t take that drug (DP, male 50-60).

Another woman described how she would normally quiz her GP on newly prescribed medicines but had not done so regarding statins:

I will ask questions ... I did ask about the risks of the arthritis one. There's no reason why I shouldn't have done with the statins but didn't ... I see them as totally different and I don't know why I should be ... they are sort of separated, this is fixing this problem so I don't have to worry about it (PA, female 70-80).

Polak (2016b) explored this paradox in a paper entitled 'What is wrong with 'being a pill-taker'? The special case of statins':

The practice of pill taking itself can constitute a challenge to the presentation of moral adequacy ... Meeting this challenge involves a complex process of often calibrating often conflicting moral imperatives: to be concerned but not too concerned, over one's health; to be informed, but not over-informed; and deferential but not over-deferential to medical expertise. This calibration reflects a broader tension between rival tropes: embracing medical progress and resisting medicalisation.

People generally identified themselves as healthy and trying to live a healthy life. It may be the case that people who adhere to statin therapy tend to be people who are more predisposed to the 'Healthy User Effect' (Brookhart et al., 2007), behaving in a broad spectrum of behaviours consistent with a healthy lifestyle. Many of the patients interviewed described in detail their fitness or diet regimes and Polak (2016b) reported similar findings whereby patients emphasise their 'virtuous adoption' of healthy lifestyles alongside the need to take statins, and so distinguish themselves from other people who are 'lazy pill-takers'. However, I also found contrasting stances; some patients reported that by taking statins they could balance out 'unhealthy' behaviour such as eating the wrong foods:

My diet would be a problem and I'm not willing to change that at the moment ... But it was a trade-off yes... I will either have to stay on them or change my diet to keep the cholesterol under control... At the moment it's easier for me to do it with a statin (KM, male 50-60).

I mean people come in with high cholesterol and you say ‘you need to give up cigarettes’.... ‘I can’t do that’ ... it’s easy to take a tablet each day from the doctor, I can still have my chips and I can still watch TV for ten hours a day and I don’t take exercise and I still smoke. But the pill is going to fix me (CS, male GP 50-60).

While this trade-off could be interpreted as a rejection of the CVD regime, it may in fact be a precise example of the actions of the ‘rational actor’ implicit in governmentality studies who is ‘capable of acting in a strategic fashion by linking decisions with actions’ (Crinson et al., 2007). The actions of people who used this strategy seem reasonable in the context of the socially accepted representation of CVD prevention. One consultant endocrinologist was explicit about this trade-off and explained his support of statin use as a pragmatic offsetting of unhealthy modern lifestyles.

GPs tended to describe candidates for statin therapy and differentiate between types of people who were suitable. When asked, GPs identified those with higher socio-economic status and education as more likely to take and adhere to statins. Goldman et al. (2006) found that highly educated people are more likely to know their total cholesterol numbers and Berglund et al. (2013) found that they have fewer concerns about medication than those with less formal education. Others have reported that those with more years of formal education are more likely to ‘know their numbers’ (Moynihan, 2011) and to ‘quantify their body’ (Lupton, 2013). Heyman et al. (2013) suggest that ‘faith in prevailing risk delineations correlates with height of position in societal hierarchies’, perhaps this group can ‘least afford to doubt the prevailing ‘regime of truth’’. Conversely, GPs stated they were more likely to prescribe for lower socio-economic patients, who ‘end up in bother more’, perhaps because some social classes are deemed as less governable in terms of adopting healthy lifestyles, as noted by one GP who said ‘I would be more inclined to go for a table there’. Women, particularly middle-aged women were more likely, according to GPs, to be concerned about their health and in particular their cholesterol levels. This may be part of the ‘Healthy User Effect’ as described above, requesting statins being just one example of ‘healthy’ behaviour (Brookhart et al., 2007). However, women’s bodies may be ‘dedicated to the collective, rather than personal well-being’ (Angus et al., 2005); their responsibilities as caregivers for others and the need to

‘be around’ to look after children and grandchildren may make women more available for medical scrutiny and to be the ‘main targets’ of medicalisation (Riessman, 1983, Nettleton, 1996):

Women seem to be more concerned about their cholesterol ... most of them have families or young grandchildren or young children themselves and they sort of see a need to be around for a bit (MK, male GP 40-50).

In the context of a governmentality analysis, individuals identified themselves, and others, as particular types of individuals or subjects within the prevailing disease regime. Patients mainly identified themselves as candidates for statins from positions of empowerment or consensus with the doctor’s position, or as those who submitted to medical power. They described taking statins as a method of trying to be healthy in conjunction with a healthy lifestyle or of trying to counteract an unhealthy one. Many expressed a dislike of taking medicines but justified taking statins as different to other unnecessary medicines, thereby positioning themselves as moral and responsible people. Doctors differentiated between candidates for statins, seeing the higher socio-economic groups and women in particular as more likely to be compliant. There was widespread ambivalence among both patients and doctors about the use of statins, but many submitted to the prevailing ‘regime of scientific veridiction’ despite these reservations.

## **7.4 Limitations**

This study offers an exploration of the assumptions, established ways of thinking and accepted practices of the Irish CVD regime. The main limitation is that the sample size is small, comprising 20 people and these are not homogeneous as they include members of the public, GPs and clinical opinion leaders. In addition, participants appeared to come from similar socio-economic backgrounds and, as noted, there may have been an element of selection bias, that is, those more interested in the subject may have been more likely to volunteer for interview. Because of this, the findings may not be generalisable to the larger statin-eligible community or prescribers. However, as noted in Chapter 6, the literature in this area tends not to distinguish between primary and secondary prevention individuals, or between the attitudes and reported behaviours of doctors to those in the primary prevention category compared to the secondary prevention category. Thus, this

chapter offers an initial inquiry into this potentially rich area of scholarship. Follow-up research with larger sample sizes may be necessary.

The study identified a number of issues of interest, some of which were motivated by earlier chapters in the thesis. These included, for example, the difference in the proportion of male statin-users compared to female statin-users who were taking statins and the issue of socio-economic disparities, which arose with some GPs. In addition, the neo-liberal nature of governmentality in Ireland was used to frame the discussion. Although these questions were addressed to some extent, it was not possible to examine them in any great detail. These topics are very broad and would warrant further more detailed analysis.

As with all qualitative research, the perspective of the researcher may lead to subjectivity; those data that interested me may have led to a greater emphasis upon them than would have been placed by another researcher. For the same reason, it is possible than some lines of enquiry were not followed that could yield rich data. Accordingly, rigour in qualitative research can be difficult to maintain, assess and demonstrate (Anderson, 2010).

Finally, for participants, the presence of the interviewer and expectations about the researcher's own perspective may have influenced their responses (Anderson, 2010).

## **7.5 Conclusions**

I have shown how a disease regime has been created around CVD prevention despite widespread ambivalence about taking and prescribing statins. Patients and doctors were concerned about over-use, about the implications of being 'a medication man' and about the undue influence of the pharmaceutical industry, for example. Despite this, in practice, there was very little actual disruption of the prevailing disease regime; patients usually took, and GPs usually prescribed, statins despite misgivings. Neither of the two patients who refused statins completely rejected the biomedical framing of cardiovascular preventative strategies. The WPR method of analysis, informed by Foucault's theory of governmentality, was useful in this context. I identified how the problem, high cholesterol, has been reified as a distinct current 'disease' requiring medical intervention.

There was some evidence of a moral discourse at play; patients often identified themselves as ‘good’ because they looked after their health, eat the right foods, exercised and took their statins. Doctors in some cases engaged a pejorative moral discourse of ‘cajoling’ patients and offering ultimatums in terms of personal behaviours.

My study took place in an Irish context and my interviewees were almost exclusively Irish. As noted, health policy in Ireland exhibits key characteristics of neo-liberal governmentality whereby responsibility for health has been allocated to the responsible, informed citizen, as well as the agent of state health policy, in the person of the GP, who nudges the patient towards behaving in an appropriate way. Although some doctors mentioned disparities in socio-economic circumstances of their patients, the focus of their practice in this context was that of the individual and not societal inequities. The problem with the construction of the individual as the sole focus of risk is that the socio-economic determinants of health in Ireland and similar neo-liberal countries may become obscured. Rockhill (2001) has noted that people in the lower socio-economic strata may be less likely to have the psychological, social and economic resources needed to alter the factors contributing to their ‘personal risk’.

I conclude that taking statins for life to prevent CVD is a common biomedically sanctioned experience in Ireland indicating that this has been a site of medicalisation displaying all the hallmarks of governmentality as described by Foucault. However, ambivalence and negotiation abounded within this prevailing authoritative discourse, indicating a complex ‘muddling through’ by doctors and patients in the face of uncertainty. The reservations of both patients (who continue to take statins despite reservations), and doctors (who continue to prescribe despite reservations), seems to indicate that even in the face of widespread ambivalence, governing can be successful.

# **8 Discussion and Conclusion**

## **8.1 Introduction**

This chapter discussed the main findings and conclusions of this thesis. To begin, Section 8.2 presents and interprets the key findings from each chapter and describes how they relate to the specific research objectives as set out in Chapter 1. In Section 8.3 the limitations of, and the overall challenges faced in, this thesis are described. The potential impacts of this thesis on health research, policy and services, as well as on society more broadly, are then outlined in Section 8.4, while Section 8.5 presents some final concluding remarks.

## **8.2 Summary and Interpretation of Findings**

In this thesis I presented a body of research on the issue of medicalisation, which has significant implications for resource allocation in health and health care, as well as for contemporary meanings and experiences of patient-hood. Primary prevention of cardiovascular disease (CVD) through the use of statins was used as an exemplar of the process of medicalisation. The overall aim of this thesis was to explore medicalisation in this context from the perspective of society as a whole, as well as from that of the individual, and to examine if it is possible to demarcate the thin line between the appropriate use and overuse of medicine.

Overall the thesis had six specific objectives, that I addressed through six chapters (Chapters 2 to 7), following a logical chain of evidence so that this overall aim could be realised. Firstly, in Chapter 1, the context and motivation for the research was presented including current policy and trends, as well as some of the debates that surround statin use. In addition, the methodology, research design and methods used throughout the thesis were described and justified. In Chapter 2 I outlined the medicalisation literature; the key concepts and process of medicalisation, the main actors within that process, the critiques of medicalisation, how statins for primary prevention of CVD exemplify this process and, finally, how to distinguish between medicalisation and overdiagnosis. In Chapter 3, statin use was quantified and the factors associated with their use, particularly in primary prevention, were analysed. In Chapter 4, the evidence to support this use was

explored, extricating those data that referred exclusively to primary prevention of CVD. Thus, in these two chapters, the current use of statins, and the current evidence to support that use, were presented. In Chapter 5, a broad illustration of the impacts of one driver of the medicalisation process was presented, that is, the expansion in the number of people considered eligible for statin therapy according to changes in clinical guideline recommendations. The impacts of this were considered from both societal and individual perspectives. Following this, Chapters 6 and 7, which are closely related, considered statins from a qualitative perspective. Chapter 6 comprised a literature review on how preventative health, risk and ‘candidacy’ for statin treatment are perceived and negotiated by doctors and patients. This chapter informed the design and focus of Chapter 7, which was a qualitative exploration of statin use in Ireland. What follows now is a more detailed review of each chapter, as well as an interpretation of the key findings from each chapter.

Chapter 2 outlined the genesis and trajectory of the concept of medicalisation and reviewed the work of key authors and themes. The first step in medicalising an issue is to recognise it as a medical problem and to use a medical vocabulary and ideology to define it. In this way, medicalisation occurs at a conceptual level. Following that, a medical solution is proposed and endorsed. Indeed, some writers have theorised that the existence of a drug in itself can stabilise the notion of the disease and become fundamental to the definition of that disease. Currently, preventative health and the management of risk are central to medical discourse. This has resulted in the normalisation of people being subject to surveillance of risk factors that *may* contribute to the development of disease, such as cholesterol levels in the case of primary prevention of CVD. Many clinical interventions, including statins for primary prevention of CVD, now base their evidence of efficacy on measurements of their impact on surrogate endpoints such as cholesterol levels, rather than on hard outcomes such as cardiovascular events like myocardial infarction (MI) or stroke. These measures are by their nature distributed along a continuum where one extreme represents a level of abnormality that justifies treatment. A key factor in the process of medicalisation has been the shifting of the demarcation line between what is considered normal and abnormal. I identified several ‘actors’ in Chapter 2, whose acceptance or rejection of the prevailing biomedical regimes of truth contributes to the process of medicalisation. These include the pharmaceutical industry, the medical profession, patients, media and marketeers, and

government and regulators. The identification of such players motivated a literature review and qualitative analysis of some of these players' experiences and perceptions subsequently in Chapters 6 and 7.

In addition to outlining the medicalisation process in general, in Chapter 2 I also described how this relates to the genesis and development of the concept of high cholesterol and the development of a drug to treat this problem – statins. With the decline of infectious diseases in the early 20<sup>th</sup> century, the focus of medical attention turned to the significance of chronic disease as a threat to public health. The statistical association between cholesterol and CHD was established by The Framingham Study in 1957, thus identifying a 'risky' surrogate endpoint, high cholesterol, as a 'legitimate' medical problem. In 1984, a major study of a cholesterol-lowering drug reported a slim margin of difference between placebo and treatment groups in the reduction of CHD (Rifkind, 1984). Although the trial included only middle-aged men with high total cholesterol levels, the authors recommended that the trials' implications be extended to other age groups and women. In this way, another characteristic of medicalisation occurred, that is, the widening of disease definition to include people outside of the trial's remit. Critics have described how consensus on the acceptance of high cholesterol as a legitimate medical problem was 'manufactured' at the time, despite many physicians contesting the validity of this trial. The subsequent development of the first statin, lovastatin, inculcated the idea of statins as an accepted medical solution to the problem of high cholesterol and motivated the development of clinical guidelines on the prevention of CVD. Over time, these guidelines changed and expanded the number of people eligible for statin treatment, a process central to medicalisation, and which motivated more detailed consideration in Chapter 5.

Finally, in Chapter 2, the boundaries between the appropriate use and overuse of a medicine, and the challenge of how to define and circumscribe overdiagnosis, were discussed. The first step in extricating whether, and in what circumstances, the medicalisation of primary prevention of CVD through the use of statins represents overdiagnosis, was to explore how statins are used in Ireland and by whom.

To this end, Chapter 3 examined the prevalence of statin utilisation of a nationally-representative sample of individuals aged over-50 years in Ireland. I found that almost one third of this cohort were using statins and, of those, almost two-thirds were doing so for primary prevention of CVD. Moreover, while just over a half of men who took statins did so for primary prevention, almost three quarters of women did likewise. In terms of the determinants of statin use, statin use increased with age, unsurprisingly, and it was also associated with living with a spouse or partner, compared to living alone. Polypharmacy and higher numbers of GP visits were also correlated with statin use. In order to further analyse who were using statins, and for what diagnostic indication, patients were classified into a hierarchy of indications that implied an ordering of priorities for treatment as described in European guidelines. In other words, those at the 'lower' end of the hierarchy, for example, whose only CVD-related diagnosis was 'high cholesterol', would have been expected to have the lowest odds of using statins. However, the analysis showed that the likelihood of using a statin did not exactly follow this order of prescribing priorities. Both 'high cholesterol' and 'diabetes' were found to have higher odds than warranted according to the hierarchy. In addition, there was no difference in statin utilisation between those above and below the risk threshold at which statin treatment could be warranted and a person's baseline risk category was not statistically significantly associated with statin use. These findings suggest that there may be an overemphasis on high cholesterol as a single risk factor as a reason to prescribe, rather than prescribing based on overall risk assessment.

Overall Chapter 3 raised several issues that informed the design of subsequent chapters. For example, the high proportion of statin users who fall into the primary prevention category and the difference between genders in terms of statins use suggested that analysis of the evidence base to underpin statin use from exclusively primary prevention data, as well as that data stratified by gender, would be useful. In addition, the possibility that high cholesterol was used to motivate statin prescribing, rather than overall risk assessment, were identified as an issue that could be explored in the qualitative research.

Having established how statins are used in Ireland and the high proportion of primary prevention users, the next step was to examine the evidence that underpinned that use. Chapter 4, therefore, comprised an overview of systematic reviews of exclusively

primary prevention data regarding the effectiveness of statins for the primary prevention of CVD. On the basis of the inclusion criteria, only three reviews were considered. One review reported a significant reduction in all-cause mortality, but no significant reductions were found in the other two reviews for this outcome. However, when this outcome was stratified by baseline risk profile, non-significant reductions were reported for all-cause mortality in all but one level of risk. While one would expect that the effect of statins would be seen most clearly in the outcome of vascular deaths, and while a significant reduction was reported for this finding overall, non-significant reductions were reported at all levels of risk when stratified. Significant reductions in composite outcomes were reported and mixed results for these outcomes when stratified by gender and baseline risk. Overall the overview suggests that there is mixed evidence on the effectiveness of statins in primary prevention populations, particularly in women. Given that, according to the results in Chapter 3, three quarters of female statin users fall into the primary prevention category, this finding has implications for the majority of female statin users. The decision to prescribe statins, therefore, should be considered in terms of absolute risk reductions (ARRs) for individual patients and in terms of the large numbers-needed-to-treat (NNTs) in some low-risk people from the perspective of society. The ARR is the reduction in risk of an adverse outcome, such as a CVD event, depending on a person's baseline risk of having such an event. The NNTs refers to the average number of patients who would need to be treated with a medicine to prevent one adverse outcome, for example, a CVD event.

The benefits of statins in terms of risk reductions were considered in more detail in Chapter 5. Changes in clinical guidelines for primary prevention of CVD have widened eligibility for statin therapy. To illustrate the potential impacts of these changes, the same cohort of over-50s from TILDA as in Chapter 3 was analysed to determine eligibility for statin therapy, as well as the associated potential cost of widening eligibility, based on seven consecutive European guidelines. The NNTs to prevent one major vascular event in patients at the lowest baseline risk for which each guideline recommends treatment were calculated and compared to that which patients reported is required to justify taking a daily medicine. The proportion of statin-eligible patients increased significantly to include almost two thirds of the sample by the end of the period examined, and the associated costs and NNTs rose proportionally. In other words, if these guidelines were

followed assiduously, the proportion of people taking statins would increase significantly and the State would increase its spending on statins correspondingly. However, many of those who would become eligible would comprise low-risk people and therefore NNTs would rise. In addition, fewer statin-eligible patients achieved risk reductions that they needed to justify taking a daily medicine. Thus, I argue that both the decision by the State to reimburse statins, and patients' decisions to take statins, could be better informed by NNTs.

This decision is even more complex for female patients. Throughout the analysis in Chapter 5, the relative risk reduction in major vascular events was considered to be similar across sub-groups. In fact, as shown in Chapter 4, the evidence to support statin use in women is weak, with non-significant results generally reported in all-cause mortality and major vascular events when stratified by gender, although one review did report significant reductions in total CVD in women. In this regard, I concur with Murad et al. (2014) who suggested that in this situation, a physician should consider what advice she would give to a patient if the true benefit of taking a medicine lay at either extreme of the confidence intervals (CIs) reported for an outcome rather than just the point estimate. Thus, some of the CIs reported in Chapter 4 imply that, in the worst-case scenario, taking statins would not benefit the woman at all or would put her at worse odds of having a major vascular event, whereas in the best-case scenario her risk would be reduced. This dilemma, of course, flags again the dearth of information available on the adverse effects of statins and reinforces calls to make individual patient data (IPD) available to independent researchers. Were this information available, both the pros and cons of statins treatment could be more accurately weighed up.

Thus, overall, Chapters 3, 4 and 5 quantified statin use, established which factors were associated with statin use, examined the evidence to support statin use in primary prevention, and assessed the potential impacts of changing clinical guidelines, which have driven the medicalisation process. These chapters are situated largely in the positivist stance of quantitative research methods. In Chapters 6 and 7 the thesis changed focus from methods that are quantitative in nature to methods that are qualitative in nature, moving from a consideration of 'the *how* of statin use' to 'the *why* of statin use'.

Given the large proportion of people in general and women in particular, taking statins for primary prevention, it was important to consider how preventative health, risk and candidacy for statin treatment were perceived by both patients and doctors. Chapter 6 comprised a literature review of qualitative research into statin use, from both patients' and doctors' perspectives. I found that there has been very little work focusing specifically on statins for primary prevention, or on women's experience of these drugs. The literature suggests that the 'lower the better' message for cholesterol levels has become embedded into 'what everyone knows'. It may be the case that some doctors, as well as patients, have difficulty differentiating, understanding and communicating the concept of risk, and the simple heuristic that 'high cholesterol' is a disease in its own right and requires treatment has arguably been a driver of medicalisation in this area. Thus, people may feel that taking statin is a necessity rather than an option that can be decided upon by weighing up the benefits and harms. These findings, and the paucity of research into statins in primary prevention, justified further research to try to understand why people take statins and what doctors believe about taking statins, which I undertook in Chapter 7.

The aim of Chapter 7 was to identify and explain aspects of how people subscribe to particular ways of understanding primary prevention of CVD, which I described as the 'Irish CVD regime', and the chapter was informed by findings in earlier chapters. For example, I was alert to any information that could explain why so many female statin users fell into the primary prevention category and whether high cholesterol was indeed used as a reason to prescribe statins, instead of being seen as one of several risk factors. Both of these issues had been raised by the findings of Chapter 3. The widening of eligibility for statin use over the last thirty years as described in Chapter 5 was something that I hypothesised the older GPs in this study could elucidate. I found that, rather than high cholesterol being seen as one of several risk factors that may contribute to heart disease, it tended to be reified and evaluated as a current problem. People knew their cholesterol levels in detail and used this information to establish their candidacy for statin therapy. However, while both patients and doctors largely considered the recommendations for statin use as evidence-based and scientific, considerable ambivalence was expressed about the use of statins. Some doctors expressed concern about a 'creeping medicalisation' and tensions existed between what doctors were

supposed to do and what they felt was the right thing to do in certain situations. Some patients also expressed ambivalence about taking statins. However, patients largely complied with doctors' recommendations and doctors largely complied with the recommendations of influential documents and peer-to-peer training, which are based on clinical guidelines. Doctors described trying to engage in shared decision making with their patients, and many patients said they questioned doctors on their recommendations. However, while questioning seemed to imbue the person with a sense of 'doing the right thing', most patients, even those expressing reservations about taking statins, did not choose to go against the doctor's advice and some doctors described cajoling patients to take statins.

Some patients distanced themselves from 'pill-takers' because statins were seen as a *different* kind of pill. They were represented as necessary, as part of a healthy lifestyle, and many patients felt they did not have a choice about whether to take them or not. However, some patients expressly stated that they used statins to 'balance out' an unhealthy lifestyle or diet. GPs identified more highly educated people as more likely to be informed about their cholesterol numbers, to take and to adhere to statins. Conversely, some GPs said that they would be more likely to prescribe for those lower socio-economic patients who 'end up in bother more'. Women, particularly middle-aged women, were more likely to be concerned about their health, according to doctors, which may be a result of having responsibility as caregivers to others and feeling that they need to be around to look after children or grandchildren.

While there was widespread ambivalence, among both patients and doctors about the use of statins, many submitted to the prevailing 'regimes of scientific veridiction' despite these reservations. Taking statins for life, I concluded, is a common biomedically sanctioned experience in Ireland, indicating that this has been a site of medicalisation with all the hallmarks of governmentality.

### **8.3 Study Strengths and Limitations and Research Reflection**

Although this thesis provided a thorough examination of the medicalisation process in the context of CVD prevention, it is important to acknowledge that there were limitations associated with the data and the methods used, and these were described in the respective

chapters. To complement these discussions, this section considers the challenges of conducting inter-disciplinary research with mixed methodologies, as well as the benefits of such adopting such an approach.

Increasingly, trends in healthcare research suggest a shifting ‘from disciplinary models to interdisciplinary team-based mixed methods inquiry designs’ (Hesse-Biber, 2016). Mixed methods research, as noted previously, provides the flexibility to tackle complex analytical and interpretative issues (Hesse-Biber, 2016). This thesis was very much an inter-disciplinary effort, integrating the expertise of my own disciplinary backgrounds in radiography and health economics, and those of my supervisors in economics, general practice and applied sociology. As such, many differences had to be navigated and negotiated at many levels (Hesse-Biber, 2016). Hesse-Biber (2016) notes that ‘the ability of team members to move between interdisciplinary and disciplinary modes of knowledge building- integration- is then a defining element of interdisciplinarity’. This required myself and members of my supervising team to move beyond our own discipline-specific attitudes, values, paradigms and methods. While all team members endorsed and encouraged the use of mixed methods, it must be acknowledged that there were challenges in reconciling the tensions between the methodologies employed. The greatest tension lay between the positivist approach adopted in the earlier chapters of the thesis and the post-structural approach of Chapter 7. The positivist paradigm posits that genuine, real and factual happenings can be studied and observed scientifically and empirically (Aliyu et al., 2014) and that ‘facts and values are ... separate and distinct’ (Bacchi, 2016). The earlier chapters of this thesis are situated within this positivist paradigm, for example, the results of Chapter 3 are presented as scientific proof of the prevalence of statin use in the sample of people examined. In contrast, Aliyu et al. (2014) notes that ‘the most severe rejection of positivism is to facilitate (some) form of post-structuralism’, yet this is precisely the perspective used in Chapter 7. This chapter was based upon post-structural analysis whereby the notion of truth was replaced by an emphasis on a reality that is *created* and consists of ‘socially produced forms of knowledge’ (Bacchi, 2016). Both positivist and post-structural stances were, I argue, required to fulfil the overall main aim of this research. It is worth noting that the team worked through these differences in a way that allows a consideration of the topic from a range of perspectives and disciplines that do not traditionally work together. For

example the debate we had around description of the methods has been resolved very clearly in the current description through clarification and description of the methodological approach and differences between methods.

Throughout the thesis I have emphasised that the question of whether medicalisation in this particular context represents appropriate use or overuse of medicine must be considered from both the perspective of society and from that of the individual patients. Initially, I believed that from the perspective of society, the question could be answered by purely quantitative methods. Were all the pertinent information available, arguably a threshold could be defined, where the marginal benefits of statin use outweighed the marginal costs. From this point only, would the State reimburse statins.

However, arguably all reimbursement decisions, policies or guideline recommendations would benefit from post-structural analysis. By rejecting the prevailing ‘regime of truth’, one can engage in critical analysis of what Bacchi describes as ‘successful’ issues, that is, issues that are considered to be problems that require solutions. The prevention of CVD has been identified as a health policy priority, and while a post-structural stance does not put into question the reality of this problem, it does allow the space to be opened up to ask: why is this solution to this problem prioritised, and, are there other ways of looking at this problem? I discuss this in greater detail in Section 8.4.

Similarly, both positivist and post-structural stances are useful for the individual patient or doctor. While the ‘hard facts’ such as baseline risk, relative risk reduction, absolute risk reduction and confidence intervals can be used in the process of shared-decision-making, the post-structural perspective has its place too. As noted in Chapter 7, while much ambivalence was expressed by both GPs and patients about using statins, their uneasiness seemed to be trumped by the ‘scientific’ nature of the prevailing wisdom that statins should be prescribed for those with ‘high cholesterol’. Thus, treating high cholesterol with statins can be seen as a ‘successful’ health policy. However, one older GP described a ‘pendulum’ whereby new treatments are enthusiastically adopted but gradually lose their popularity over time. This statement hints that he is aware that in some way health problems are ‘constructed’ and ‘culturally, spatially and historically specific’ (Klawiter, 2004). Contrary to the positivist stance, facts and values may not,

perhaps, be considered as separate, and may free people to act in concordance with their own values rather than subscribing to the ‘prevailing truth’ of the time.

Thus, there is value in both positivist and post-structural stances and I argue their differences added to the richness of this thesis, even though they draw on fundamentally different understandings of reality. In the following section I will describe the potential impacts of this thesis and how both the positivist and post-structural paradigms can contribute to research, policy, health service and society more generally.

A cross-cutting limitation throughout this thesis related to a lack of access to data specifically regarding primary prevention of CVD. I found that secondary and primary prevention tended not to be disaggregated in trials, systematic reviews and in the qualitative literature that examined attitudes to statins. In addition, each study within the thesis was subject to additional specific limitations relating to data and methods, as detailed in each chapter.

In summary, in Chapter 1, the trends in statin reimbursement in Ireland outlined statin use in those covered by the GMS scheme but not by those paying privately for statins. The costs of statins over time would warrant deeper analysis accounting for generic substitution and price negotiations between payers and the pharmaceutical industry. In addition, it was not possible to explain the decrease in statin utilisation from 2009 to the present.

As noted, the findings of some studies within the thesis informed the design of subsequent chapters, as well as revisions of earlier chapters. For example, the finding in Chapter 3 that there was a difference in statin use between genders motivated a consideration of this issue in the literature review in Chapter 2 as well as a greater focus on the evidence base for statins in women in Chapter 4. However, some themes arose would justify detailed analysis and discussion, which was beyond the scope of this thesis.

Chapter 3 had a number of limitations relating to both data and methods, which are described in detail in the chapter. These included the limitation of self-reported doctor diagnoses by participants and possible recall bias. Some diagnostic categories could not be defined due to limitations of coding in the TILDA database. In addition, it was not possible to ascertain which participants might previously have been taking statins but

who discontinued; this would impact their reported LDL and TC levels, which were used to calculate their SCORE.

The overview of systematic reviews in Chapter 5 was limited firstly by the type of data reported in the included reviews; both IPD and aggregate trial data were reported. Thus, meta-analysis of the findings was not possible. In addition, some relevant reviews may have been excluded because I could not ascertain the proportion of primary data within them.

Chapter 5 was designed to illustrate the potential impact of changing clinical guidelines. Four potential impacts were identified; the proportions of people eligible for statins; costs; NNTs; and levels of risk reduction that are ‘acceptable’ to patients. The chapter was designed to illustrate these impacts rather than describe the ‘real-world’ empirical detail of each. For example, I used a weighted average cost per statin to examine the potential cost increases associated with increased statin eligibility. However, statin costs have fallen substantially in recent years, partly due to the termination of statin patents. Furthermore, the types of statins used and dosages could not be examined from these data. As with Chapter 3, estimation of patients’ baseline risk was complex as some of the sample may have been previously taking statins, thus impacting their LDL and TC levels. The heterogeneous nature of the patient preferences reported in the systematic review I used to inform this study made it difficult to identify a specific level of risk that patients would find acceptable to justify statins use. Indeed, it is possibly the case that such value judgements are unique to each individual patient and their doctor.

The literature identified in Chapter 6 did not distinguish, for the most part, between primary and secondary prevention of CVD. While this clearly identified a research gap, and therefore justified the qualitative research I undertook in Chapter 8, the presentation of emerging themes differed according to the differing disciplinary orientations of the journals from which the studies were selected. These were classified as ‘medical’, ‘sociological’ or ‘psychological’ in nature. Because of this, and because most did not distinguish between primary and secondary prevention participants, there may be limitations to the findings of this chapter.’

Finally, the sample size in Chapter 7 has, as noted, limited the generalisability of the findings. Several themes emerged during the study that would warrant greater analysis,

which were beyond the scope of this study. However, I hope that identification of these interesting themes may lead to further research in this area.

## **8.4 Impact**

According to the Research Impact Framework (Kuruville et al., 2006), the impacts of health research can be considered under four broad headings: research-related impacts; policy impacts; service impacts; and, societal impacts. However, these impacts cannot be considered mutually exclusive categories, rather an overview of ‘potential and sometimes overlapping research areas’ (Kuruville et al., 2006). In this section, I describe the way in which this thesis might influence and impact upon health research, policy, service and society in general. Under each of these four key areas, I consider some of the descriptive categories identified by Kuruville that are relevant to this thesis and how the methods used, and findings of each chapter, may impact each of these areas.

### **8.4.1 Research Impacts**

Kuruville et al. (2006) describes several categories that can be used to assess the impacts of one’s research on the field of research itself. This can include generating data about a problem or evidence of effectiveness of an intervention, addressing research gaps, contributing to ethical debates and guidelines, and responding to topics of public interest. In addition, the application of established methods to new areas of research can have an impact on the field of research. Finally, the impact of research is most commonly described in terms of publications and presentations. This subsection outlines how each of these impacts arise in my research.

This thesis considered the problem of how to delineate between appropriate use and overuse of a medicine. It has been suggested that when researching the overuse of medicine, certain steps need to be undertaken. These include estimating the frequency of overuse, identifying the factors promoting overuse and estimating the effects of overuse (Morgan et al., 2015). Each of these steps have been undertaken in this thesis within separate analyses that comprise Chapters 3 to 7. In each, data have been generated from these studies, the evidence of effectiveness has been analysed, and research gaps have been identified that may influence future research.

The basis of this thesis is the concept of medicalisation and there have been calls to examine medicalisation within specific contexts. Thus, I have addressed a research gap by chronicling the process of medicalisation in the context of statins for primary prevention of CVD, a topic of considerable and ongoing public interest. In addition, I have strengthened the argument that trying to establish the boundary between medicalisation and overuse in specific healthcare contexts should be prioritised in health research. The importance of this will be considered when discussing the policy and societal impacts of research below.

In Chapter 7 a post-structural method of analysing qualitative data was used. This, as far as I am aware, was the first application of the post-structural ‘What’s the Problem Represented to Be?’ (WPR) method to this field and may encourage other researchers to incorporate such an approach to other areas of research. In addition, the overall methodological paradigm of the thesis, that of eclecticism, and the use of mixed methods may be useful for other researchers in tackling medicalisation in other contexts.

Finally, the findings of this thesis have been disseminated through articles published in (or submitted to) peer-reviewed international journals, as well via conference presentations both in Ireland and internationally. More specifically, my thesis outputs to date include the following:

#### *Journal Articles*

1. Byrne, P., Cullinan, J., Murphy, C. & Smith, S. (2018). Cross-sectional analysis of the prevalence and predictors of statin utilisation in Ireland with a focus on primary prevention of cardiovascular disease. *BMJ Open*, 8, e018524.
2. Byrne, P., Cullinan, J., Smith, A., & Smith, S. (2019). Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews. *BMJ Open*, 9, e023085.

3. Byrne, P., Cullinan, J., Gillespie, P., Pereira, R., & Smith, S. (2019). Statins for primary prevention of cardiovascular disease: modelling guidelines and patient preferences. *British Journal of General Practice*. Doi:bjgp19X702701.
3. Byrne, P., O'Donovan, Ó., Smith, S. & Cullinan, J. (2019). Medicalisation, risk and the use of statins for primary prevention of cardiovascular disease: a scoping review of the literature. Revisions submitted to *Health Risk and Society*.
4. Byrne, P., O'Donovan, Ó., Smith, S. & Cullinan, J. (2019). Medicalising and governing the prevention of cardiovascular disease: A qualitative exploration of the prescribing and usage of statins in Ireland. Revisions submitted to *Sociology of Health and Illness*.

#### *Other Publications*

1. Byrne, P., Cullinan, J., Smith, A., & Smith, S. (2017). Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews. PROSPERO: International Prospective Register of Systematic Reviews. doi: 10.15124/CRD42011100485. Available from: [www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=42011100485](http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=42011100485).

#### *Conference and Seminar Presentations*

##### Oral Presentations

1. Byrne P, Cullinan J, Gillespie P, Perera R, Smith SM. Statins for the primary prevention of cardiovascular disease: a simulation of eligibility, costs, patient preferences and number-needed-to-treat in the context of changing clinical guidelines. Preventing Overdiagnosis 2018, Copenhagen 20-22nd August 2018.; 2018.
2. Byrne P, Cullinan J, Gillespie P, Perera R, Smith SM. Expanding the boundaries of statin treatment-is it worth it? Cost implications and acceptability to patients.

SPHeRE Network 4th Annual Conference, RCSI, Dublin, 11th January 2018.; 2018.

3. Byrne P, Cullinan J, Murphy CM, Smith SM. Who use statins and why? A cross-sectional analysis of statin utilisation in the context of cardiovascular risk and socio-demographic factors. Presented at:
  - (i) Preventing Overdiagnosis Conference, Barcelona, 20-22 September 2016.; 2016
  - (ii) The Brown Bag Seminar, September 2016, Discipline of Economics, National University of Ireland Galway, Galway, Ireland
  - (iii) The Irish Longitudinal Study on Ageing, Cardiovascular Disease Group, October 2016, Trinity College Dublin, Ireland

#### Poster Presentation

1. Byrne P, Cullinan J, Murphy CM, Smith SM. Who use statins and why? A cross-sectional analysis of statin utilisation in the context of cardiovascular risk and socio-demographic factors. SPHeRE 3rd Annual Conference, RCSI, Dublin, 12th January 2017 - Winner of Best Poster, 2017.

#### **8.4.2 Policy Impacts**

One of the main objectives of health research is to inform and influence policy. Again, Kuruvilla et al. (2006) describes how research can influence policy. Firstly, by providing persuasive evidence, research can raise awareness and mobilise support for new policymaking. Secondly, research can lead to new concepts, ideas or language that influence the nature and substance of policy discourse. Thirdly, existing beliefs and practices may be changed or transformed because of research findings. Finally, by participating in policy networks with particular interests or perspectives, a researcher can influence those networks and be influenced by them.

This thesis has identified a topic of considerable importance to the healthcare system, that is, the overuse or low-value use of medicine, and the evidence presented here may raise awareness of this issue. Overuse of medicine has been largely overlooked by Irish

policy makers, and with the exception of antibiotics, to date governments in general have not looked carefully or critically at the issue of the overuse of medicines (Busfield, 2015). In Ireland, the focus of health care reform and future development has been centred on a report by the Oireachtas Committee on the Future of Healthcare called Sláintecare (Burke et al., 2018), whereby:

... in future, everyone has access to an affordable, universal, single-tier healthcare system, in which patients are treated promptly on the basis of need, rather than ability to pay ... This ... represents a new vision for the future of healthcare in Ireland (Committee on the Future of Healthcare, 2017, p.4).

The report notes that ensuring value for money and accountability for spending are a fundamental principle of reform. Waste in pharmaceutical spending is recognised, but this is to be countered, by ‘reducing the volume of unused medicines, increasing the use of generics or biosimilars, and seeking opportunities for lower prices through more effective procurement processes’ (Committee on the Future of Healthcare, 2017, p.99). Only two sentences in the report refer to ‘the negative implications of overprescribing’ and while the Committee ‘considers there is a need for appropriate oversight and audit of prescribing and dispensing patterns’ no further detail is offered about how to go about this (Committee on the Future of Healthcare, 2017, p.99). Indeed, in the section of the report dealing with the cost of implementation of reforms, no mention is made of the reduction in over-prescribing as a cost-saving measure. Although the report notes Ireland’s high spending in health care (Committee on the Future of Healthcare, 2017, p.118), and that this raises questions about value for money, overprescribing is not listed as a possible cause of high spending. The publication of the report generated substantial media attention, much of which was concerned with the cost of reforms. However, as far as I am aware, addressing overuse of medicine and low-value care has not been considered part of the solution to this (O’ Cionnaith, 2018, Wall and Kelly, 2018).

In contrast to Ireland, attempts have been made in other countries to quantify ‘low-value services’ in health care. The Washington Health Alliance, for example, recently published a report documenting that 44% of services provided were determined to be ‘wasteful’. This equated to \$258 million, or 33% of total spending on health care services,

in the state of Washington. This report urges that the issue of overuse is ‘central to discussions of health care value’ and that ‘(q)uestioning the value of medical tests and treatments needs to become an integrated ...part of medical training’ (Brown and Clement, 2018). If a similar audit were undertaken in Ireland, this thesis could motivate analysis of current spending on statins. The question could be posed as to whether some of the €50million currently spent from the public purse on statins could be better spent attempting to deal with the socio-economic determinants of CVD, for example, and if so, how could those in authority go about setting such an agenda? Thus, the thesis provides ‘persuasive evidence to ... raise awareness and support for new policy-making’ (Kuruvilla et al., 2006).

However, mobilising support for a new type of policy making in health care would require changes in the ‘concepts, ideas or language that influence the nature and substance of policy discourse’. I argue that the concept of overuse and low-value care should become integral to policy making, particularly in the context of reforms advised by Sláintecare. With regard to statins, Melzer and Zimmern (2002) have noted that ‘even if treating individuals with statins is beneficial, for a health system, the cost of achieving these benefits among a minority of patients who avoid serious events is staggering, and the resources consumed may be better used elsewhere’. The most recent CVD policy document in Ireland encourages people to ‘know their numbers’ in terms of cholesterol levels and advocates educational campaigns to achieve that aim (Department of Health & Children, 2010, p.68). If such campaigns were to be undertaken, the concepts of prescribing on the basis of overall CVD risk and absolute risk reduction could be simplified and incorporated. Public campaigns have been undertaken, for example, to counter the over-prescription of antibiotics (Jones, 2011).

Throughout this thesis I have attempted to examine how the boundaries between appropriate use of and overuse of statins could be established. This aim, the step-by-step approach, as well as the various methods employed to achieve it, could be used as a template for other areas of prescribing. The thesis followed a logical chain of analysis establishing first who are using statins and why, the evidence underpinning that use, the impact of changing clinical guidelines, and finally examining the human perceptions and experiences that drive statin use and prescribing behaviour. While I agree with Brown

and Clement (2018) that low-value care is deeply ingrained in medical practice and within our culture, by undertaking a similar analytic approach in other therapeutic areas, existing beliefs and practices could be challenged.

Finally, I have contributed to a wider policy network by attending the Preventing Overdiagnosis conferences in 2015, 2017 and 2018, where I presented some studies from this thesis. The aim of the Preventing Overdiagnosis conferences is to ‘improve understanding of the problem of overdiagnosis’ (Moynihan et al., 2012). By contributing to, and networking within, this ‘epistemic community’ (Kuruville et al., 2006), I have contributed to and been informed by the development of ideas and interests within this subject area. As a result of one such presentation, I have been invited by Fiona Godlee, editor of *The BMJ* to write an opinion article for the journal on statins for primary prevention, based on the findings of Chapters 4 and 5.

### **8.4.3 Service Impacts**

Research can impact health services by contributing to evidence-based practice and quality of care by providing information on the efficacy of health intervention and the acceptability of interventions provided (Kuruville et al., 2006).

Firstly, the findings of this thesis can contribute to the evidence-base of day-to-day medical practice. For example, contrary to other analyses, I found no statistically significant evidence of the benefit of statins on all-cause mortality and other outcomes when participants were stratified by their baseline risk. Thus, knowing a person’s absolute risk reduction is of far more relevance than knowing their relative risk reduction from taking statins. In addition, when reported risk reductions are not statistically significant, there may be no benefit at all in taking statins and the possibility arises that a patient would be worse off by taking the medicine. These findings highlight the importance of shared decision making (SDM), as patients will view such information on the basis of their personal values. For some, any reduction in risk of CVD, no matter how small, is worthwhile. For others, a small risk reduction will not outweigh the possibility of harm or the disutility of taking a medicine daily. As noted by Callahan (2009, p.160):

If patient self-definition is allowed to rule, then the notion of ‘benefit’ is strictly for the patient to determine and will be helped along by the physician who believes that individual patient benefit and physician judgement trump all other values.

However, SDM can be challenging in the context of busy GP practices. Barriers to SDM have been noted and include time constraints, a lack of applicability due to patient characteristics and lack of applicability due to the clinical situation (Gravel et al., 2006).

#### **8.4.4 Societal Impacts**

Kuruvilla et al. (2006) also outlined how research impacts can be described in terms of impacts at a societal level. Research can influence human rights by reinforcing the right of individuals to participate in decisions that influence their lives and the right to information on the same. Secondly, research can contribute to self-efficacy and collective efficacy, described as the ability and resources for problem solving at individual and societal levels. As noted earlier, Brown and Clement (2018) have called for a cultural change in medical care to reduce overuse of established low-value services, but that:

The excessive use of low-value health care services may be too deeply ingrained in medical training and culture to be sustainably reduced by the available interventions applied in an environment that is geared to doing more testing and treatment.

It has been argued that teaching people how to assess the trustworthiness of claims about medical treatment would improve the well-being of patients and the public in general (Chalmers et al., 2018). Concepts such as NNTs, ARRS and SDM, whose importance have been highlighted throughout this thesis, enable individual patients to fully participate in decisions that affect their lives and health.

In addition, this thesis has emphasised the profound influence a prevailing biomedical belief system, shaped by the political and social norms of the time, can have. The Sláintecare reforms, for example, are predicated on the assumption that health care spending *must* always rise, particularly in line with an ageing population. However, there

may be other ways of conceptualising an ageing population that incorporate the values of older people:

Most concepts of successful ageing are used uncritically ... While the biomedical models emphasised the absence of disease and good physical and mental functioning as successful ageing ... sociopsychological models emphasised life satisfaction, social functioning and participating or psychological resources ... There is little point in developing policy goals if elderly people do not regard them as relevant ... The medical model is so dominant that few health professionals are aware of psychosocial ageing. The result is a focus on the burden of old-age, the decline and failure of the body (Bowling and Dieppe, 2005).

Although almost half of over-75s analysed in Chapter 3 were taking statins, Albarqouni et al. (2017) reported that only 3% of community living older people would agree to a medication with adverse effects that could affect their activities of daily living and half would not agree to take the medicine if it was associated with even mild fatigue or nausea. It is possible that many older people would refuse statins, were they fully informed about the risk reductions relevant to them, particularly if data on the harms of statins were made available.

Thus, overuse of medicines and low-value care are social and ethical problems, not just scientific ones (Carter et al., 2015). As such, developing strategies that promote public debate about the inherent uncertainty and limitations of healthcare, as outlined in this thesis, would be beneficial.

## **8.5 Further Research**

This thesis explored the delineation of appropriate use and overuse of statins in primary prevention. This is a broad theme, which has been debated for decades and which continues to be topical (Armitage et al., 2019, Hawkes, 2019). Using mixed methods, I have provided a strong analysis of this problem and suggested ways in which it could be elucidated and addressed. Nonetheless, the thesis has also identified areas that would warrant further research.

For example, the literature review on medicalisation identified key ‘actors’ in the medicalisation process. These are people, or institutions, that impact how a problem becomes a medical problem and how a medical solution is identified and accepted by society. It would be useful to develop a theoretical framework about these main contributors to medicalisation. As I noted in Chapter 2, separating these actors as if they were discrete players within the process is useful for analytical purposes but in reality, each interacts with the other, reinforces the others’ position or disrupts it. Ultimately, it is these interactions, rather than the actions of any one type of actor that creates the prevailing, consensual regimes of truth that enable medicalisation.

I have concluded that statin use should be predicated upon a person’s baseline level of risk, the potential absolute risk reduction (ARR) from taking statins, as well as their own preferences in terms of acceptable risk reductions. All of these processes take time, time that can be scarce in a busy general practice. It would be useful to examine the increased workload and resource implications entailed in fully assessing patients’ preferences and ARRs as required to enable implementation of these findings. Arguably there is potential for the development of decision aids for doctors in this context. For example, computer-based decision support systems (CDSSs) have in some circumstances helped doctors reduce inappropriate prescribing. One systematic review of the subject found that CDSSs that automatically provided decision support were more likely to improve prescribing practice in contrast to systems that had to be actively initiated by healthcare providers (Holstiege et al., 2014). In addition, from the State’s perspective, in an ideal world, only statins with NNTs or ARRs above a certain agreed level should be reimbursed. This would require health technology assessment or cost-effectiveness analyses stratified by baseline risk, NNT or ARR. While the administrative burden of such a mechanism may be prohibitive, it would be valuable to study ways of ensuring value-for-money in reimbursement of this drug. Such a mechanism would also have relevance to other drug types.

As noted in Chapter 3, a greater proportion of females than males take statins for primary prevention. While this issue was considered in Chapter 7, it warrants greater consideration. This could entail more detailed qualitative research focusing on if, and

why, women are more willing to take statins, in the absence of symptomatic CVD, as well as the behaviour and attitudes of GPs to women in terms of preventative health.

As I have noted, particularly in Chapter 4, there are gaps in the data that are available regarding the benefits and harms of statins. Since the completion of the overview of systematic reviews in Chapter 4, the CTT have published a new analysis of the benefits of statins stratified by age. Some of the results in this review were reported according to the participants' history of vascular disease, that is, by primary compared to secondary prevention. In the primary prevention category, statistically significant reductions in major vascular events were reported for those under 70 years, however, the results for those over 70 were not statistically significant (70-75 years RR 0.84 (CI 0.70-1.01) and 75+ RR 0.92 (CI 0.73-1.16)). It would be useful if the CTT undertook analyses of their data for primary prevention stratified by age, baseline risk and sex. Alternatively, if these data were released to other researchers, such analyses could be undertaken, results estimated and made available to patients, their doctors and other researchers.

From a societal perspective, as I have argued, some statin use and reimbursement is likely to comprise low-value care and represent a waste of resources. At the same time, statin use has been normalised among asymptomatic people in modern society, thus enabling and facilitating inappropriate or low-value use. In Chapter 5, I examined how the benefits, or harms, of statins to society may have changed over time, but, as noted, while this study illustrates these trends it was not possible to fully examine the implications of rising statin eligibility in real terms. This would warrant deeper analysis of each section of my study. Of particular interest would be an analysis of actual statin usage over time in terms of the baseline risk of those taking them. However, it is likely that no such data would be available. Nonetheless, the findings of Chapter 5 could be used to illustrate to policy-makers, guideline developers, and clinical decision-makers the potential implications of unchallenged widespread statin use and may encourage them to give greater consideration to this from the perspective of over-stretched healthcare resources, opportunity costs and patient preferences.

## 8.6 Concluding Remarks

The overall aim of this thesis was to explore the medicalisation of primary prevention of CVD through the use of statins, and to examine if it is possible to demarcate the line between the appropriate use and the overuse of medicine. I have established that statins are a commonly prescribed medicine in Ireland, largely used for primary prevention of CVD, particularly in women. Their use has expanded over time and notwithstanding drops in the cost of statins, absorb a considerable amount of healthcare spending. I contend that primary prevention of CVD is a clear example of a medicalisation process and that this has been supported by changes to clinical guideline recommendations. While significant reductions in CVD outcomes were reported in my overview of systematic reviews, these reductions are not observed when stratified by baseline risk. This raises two key questions. Firstly, do the benefits of statins outweigh the costs, opportunity costs, or harms to society and to the individual patient? Secondly, how has statin use become so prevalent, given the limitations of the evidence in primary prevention.

Low-value care has been defined as healthcare that offers little clinical benefit but has the potential to cause harm (Brown and Clement, 2018) and I argue that for many patients in primary prevention, and for the State reimbursing those patients, statin use may be an example of low-value care and, in some cases, represent a waste of healthcare resources. However, the boundaries between appropriate use, overuse and low-value care are difficult to delineate, as outcomes in individual cases and patient preferences can never be accurately predicted. Of note is the lack of access to data on the potential harms of statins that has hindered independent research on this topic. The prevalence of statin use and prescribing are predicated not just on clinical guideline recommendations but also upon the human perceptions and experiences of patients and doctors. These perceptions influence how the problem of CVD prevention had been constructed not just by patients and doctors, but by policy makers and guideline developers too. Therefore, to conclude, I argue that the prescription, use and reimbursement of statins in primary prevention warrants more careful consideration incorporating patient preferences and NNTs, and that the concept of overuse and low-value care should become integral to policy making.

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# Appendices

## Appendix 1: The Indication Hierarchy

Wallach Kildermoes constructed a hierarchy of indications for which statins were prescribed. The hierarchy consisted of myocardial infarction (MI), ischaemic heart disease (IHD), stroke, peripheral arterial disease (PAD), other potential arterosclerotic disease (PAC), diabetes, primary hypertension, as well as a group with no markers of diagnosis. The cohort examined were discharged patients from Danish hospitals who had been given discharge diagnoses, according to the International Classification of Diseases (ICD). The TILDA participants, in contrast, self-reported their doctor diagnoses of the various indications and so these may not correspond perfectly with ICD or the Wallach Kildermoes hierarchy. The diagnosis peripheral arterial disease (PAD) was omitted as only those who reported heart attack were asked if they had angioplasty or stent and it is not clear whether these procedures were carried out on peripheral blood vessels or coronary. However, for the purpose of this study, the reported diagnoses are classified into a hierarchy of indication largely corresponding with that of Wallach Kildermoes.

## Appendix 2: TILDA Self-reported Doctor Diagnoses, Corresponding Hierarchy of Indications and ICD Codes

	<b>Diagnosis on the hierarchy</b>	<b>Diagnosis</b>	<b>ICD 10 code</b>	<b>TILDA self reported doctor diagnoses</b>	<b>TILDA code</b>
<b>1</b>	MI	Myocardial infarction	I21-23, I241, I252	Heart attack	ph201_3
<b>2</b>	IHD	Ischaemic heart disease	I20, I24-25 (not I241, I252, I253, I254)	Angina	ph201_2
<b>3</b>	Stroke	Stroke	I63-66, I693-94, G45-46	Stroke Ministroke or TIA	ph201_6 ph201_7
<b>4</b>	PAC	Potential atherosclerotic conditions	I50, I11-15, I34-35, I44-45, I46-49	Congestive heart failure Heart murmur Abnormal heart rhythm	ph201_4 ph201_9 ph201_10
<b>5</b>	Diabetes	Diabetes	E10-14	Diabetes	ph201_5
<b>6</b>	Hypertension	Primary hypertension	I10	High blood pressure	ph201_1
<b>7</b>	High cholesterol	High cholesterol	E78	High cholesterol	ph201_8
<b>8</b>	No diagnosis	None of the above diagnoses		None of these (none of the above)	ph201_14

### Appendix 3: Variables Used in TILDA Analysis

Variable Name	Variable Description	Recoding
Statins	Statins (ATC code C10AA and C10B)	Recoded from TILDA data which records ATC codes of medications being taken by participants. Generated variable 'MDStatins' from those drugs classified as C10AA (statins alone) and C10B (statins in combination)
Sex	Gender: Male or Female	
Education	Highest educational level achieved: Primary or none; Secondary; Third or higher	
Social class	Social class. These are classified in TILDA as variable 'SESocial_class' which has nine categories: Not applicable; Professional workers; Managerial and technical; Non-manual; Skilled Manual; Semi skilled; Unskilled; unknown and refused; Farmers. Participants were assigned to one of these categories following responses to questions regarding their job description, nature of business or occupation and farm ownership during the CAPI.	The nine social class categories described in TILDA were recoded into six social class categories: <ol style="list-style-type: none"> <li>1. =Professional workers; Managerial</li> <li>2. =Non-manual; Skilled manual</li> <li>3. =Semi skilled; Unskilled</li> <li>4. =Farmers</li> <li>5. =Not applicable</li> <li>6. =Unknown and refused</li> </ol>
Income	Describes six levels of income. The variable income5 is a recode of si408, a question in the CAPI, which asks how much total income a person earned in the last 12 months.	Recoded within TILDA from the variable si408 "How much income in total have these people received in the previous 12 months, i.e. total income of the household after tax" For respondents who provided a point estimate at si408, this value is used. For respondents who did not provide a point estimate at si408 but provided an "unfolding bracket" at si409, the information from si409 is used. The mid-point of the bracket is used, so someone answering "More than €10,000 but less than €20,000" at si409 would be assigned a value of €15,000.  The categories of income are: <ol style="list-style-type: none"> <li>1. = &lt; €10,000</li> <li>2. = ≥ €10,000, &lt; €20,000</li> <li>3. = ≥ €20,000, &lt; €40,000</li> <li>4. = ≥ €40,000, &lt; €70,000</li> <li>5. = ≥ €70,000, &lt; €2,000,000</li> <li>6. Missing</li> </ol>

Medical Insurance	Three categories describing whether the person has: No medical costs cover; Medical insurance; Medical card	
GPvisits	Number of GP visits in the previous year: 0;1-2;3-4;5-6;7 and over	Recoded from a continuous variable in TILDA (hu005) that recorded the number of GP visits in the previous year.
Polypharmacy	Polypharmacy is defined by TILDA as taking 5 or more medications, excluding supplements. This is a binary variable	I created a new polypharmacy variable which excluded statins from the medications that accounted for polypharmacy, i.e. polypharmacy is now defined as five or more medications, excluding statins
Location	Describes three categories, whether the person: Lives in Dublin city or county; Lives in another urban area; Lives in a rural area	
Lives With	Describes three categories, whether the person is: Living alone; Living with spouse/partner; Living with others	
Indication	A hierarchy of mutually exclusive diagnostic indications for which statins may be prescribed. See Appendix 1	
SCORE	Binary variable describing whether a person's risk SCORE is $< 5\%$ or $\geq 5\%$ . SCORE estimates the probability of a person experiencing a fatal coronary event within the next ten years and is used to inform decision making on interventions to prevent this, such as the prescription of a statin	Risk factors recorded in TILDA are used to calculate SCORE. These are: cholesterol level, systolic blood pressure, smoking status and age.

## **Appendix 4: Estimation of the Health Assessment Survey Weights**

The estimation of the health assessment weights is described in the TILDA report “Fifty Plus in Ireland – First Results from the Irish Longitudinal Study on Ageing” (page 300). It was calculated using the CAPI weight divided by respondents’ subsequent probability of having completed a health assessment. The CAPI weights were estimated by comparing the numbers of individuals in the sample with a given combination of characteristics with the same number in the population, estimated using the Quarterly National Household Survey (QNHS 2010). The characteristics compared were age, sex and educational attainment. The probability of attending a health assessment was estimated using logistic regression and is based on the characteristics shown to significantly affect participation in the health assessment: those with higher education; people with better health and; those in the youngest age group.

## Appendix 5: Statin Utilisation According to Age and Indication Among Female TILDA Participants (Wave 1) Aged Over 50 Years (n=3,014)

	Age	Number	Number on statins	% taking statin [95% CI]	MI	IHD	Stroke	PAC	Diabetes	Hyper-tension	High chol.	No diagnosis
	50-64	1,868	399	21.4% [19.6%-23.3%]	12	10	14	40	33	132	139	18
	65-74	747	295	39.5% [36.0%-43.1%]	13	19	20	28	23	79	95	17
	75+	399	175	43.9% [39.0%-48.8%]	18	22	14	26	12	51	20	9
	Total	3,014	869	28.8% [27.2%-30.5%]	43	51	48	94	68	262	254	44
Total with diagnosis whether on statins or not					60	74	80	277	121	730	553	1,100
% of those with indication on statins [95% CI]					71.7% [58.7%- 81.8%]	68.9% [57.3%- 78.6%]	60.0% [48.7%- 70.3%]	33.9% [28.6%- 39.7%]	56.2% [47.1%- 64.9%]	35.9% [32.5%- 39.4%]	45.9% [41.8%- 50.1%]	4.0% [3.0%- 5.3%]
% of those on statins with indication					5.0%	5.9%	5.6%	10.9%	7.9%	30.3%	29.4%	5.1%

Source: Analysis of The Irish Longitudinal Study on Ageing (TILDA) Wave 1 data.

Notes: The column 'Number' represents the total number of individuals in the TILDA dataset by age group and overall, whether they are taking a statin or not, while the column 'Number on statins' represents the total number of individuals taking a statin. The column '% taking statins' is the number on statins as a percentage of all individuals by age group and overall. The subsequent eight columns present the numbers or percentages on statins for each of the indication categories. MI= myocardial infarction; IHD = Ischaemic Heart Disease; PAC= potential atherosclerotic conditions.

## Appendix 6: Statin Utilisation According to Age and Indication Among Male TILDA Participants (Wave 1) Aged Over 50 Years (n=2,604)

	Age	Number	Number on statins	% taking statin [95% CI]	MI	IHD	Stroke	PAC	Diabetes	Hyper-tension	High chol.	No diagnosis
	50-64	1,519	366	24.1% [22.0%-26.3%]	44	19	11	33	38	95	112	11
	65-74	741	316	42.6% [39.1%-46.2%]	59	37	19	32	38	68	41	17
	75+	344	164	47.7% [42.4%-53.0%]	39	25	14	25	16	22	10	10
	Total	2,604	846	32.5% [30.7%-34.3%]	142	81	44	90	92	185	163	38
Total with diagnosis whether on statins or not					190	105	70	207	156	554	392	908
% of those with indication on statins [95% CI]					74.7% [68.0%-80.5%]	77.1% [68.0%-84.3%]	62.9% [50.7%-73.6%]	43.5% [36.8%-50.4%]	59.0% [51.0%-66.5%]	33.4% [29.6%-37.4%]	41.6% [36.8%-46.5%]	4.2% [3.1%-5.7%]
% of those on statins with indication					17.0%	9.7%	5.3%	10.8%	11.0%	22.2%	19.5%	4.6%

Source: Analysis of The Irish Longitudinal Study on Ageing (TILDA) Wave 1 data.

Notes: The column ‘Number’ represents the total number of individuals in the TILDA dataset by age group and overall, whether they are taking a statin or not, while the column ‘Number on statins’ represents the total number of individuals taking a statin. The column ‘% taking statins’ is the number on statins as a percentage of all individuals by age group and overall. The subsequent eight columns present the numbers or percentages on statins for each of the indication categories. MI= myocardial infarction; IHD = Ischaemic Heart Disease; PAC= potential atherosclerotic conditions.

## Appendix 7: Basic Search Strategy

Cardiovascular disease term
<b>and</b>
Primary prevention term
<b>and</b>
Statin term
<b>and</b>
Systematic review term

## Appendix 8: Basic Search Terms MEDLINE

Cardiovascular Disease term	<ol style="list-style-type: none"> <li>1. *Cardiovascular Diseases/</li> <li>2. cardiovascular disease*.tw.</li> <li>3. heart disease*.tw.</li> <li>4. (coronary adj2 disease*).tw.</li> <li>5. (arteriosclerosis or atherosclerosis).tw.</li> <li>6. angina*.tw.</li> <li>7. infarct*.tw.</li> <li>8. exp Stroke/</li> <li>9. (stroke or strokes).tw.</li> <li>10. hypertens*.tw.</li> <li>11. ((blood or diastolic or systolic) adj2 pressure*).tw.</li> <li>12. exp Hyperlipidemias/</li> <li>13. hyperlipid*.tw.</li> <li>14. hypercholesterol*.tw.</li> <li>15. cholesterol*.tw.</li> <li>16. hypercholesterol?emia*.tw.</li> <li>17. hyperlipi?emia*.tw.</li> <li>18. triglycerid*.tw.</li> <li>19. hypertriglycerid?emia*.tw.</li> <li>20. hyperlipoprotein?emia*.tw.</li> <li>21. ldl.tw.</li> <li>22. hdl.tw.</li> </ol>
<b>and</b>	
Primary prevention term	<ol style="list-style-type: none"> <li>28. exp Primary Prevention/</li> <li>29. (prevent* or prophyla*).tw.</li> </ol>
<b>and</b>	
Statin term	<ol style="list-style-type: none"> <li>23. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/</li> <li>24. hydroxymethylglutaryl*.tw.</li> <li>25. HMG-CoA*.tw.</li> <li>26. (statin or statins).tw.</li> <li>27. (atorvastatin or lipitor or cerivastatin or baycol or compactin or fluvastatin or fluindostatin or lescol or lovastatin or mevacor or mevinolin or pitavastatin or pitava or livalo or pravastatin or pravachol or lipostat or rosuvastatin or crestor or simvastatin or zocor).tw.</li> </ol>
<b>and</b>	
Systematic review term	<ol style="list-style-type: none"> <li>30. (MEDLINE or systematic review).tw. or meta analysis.pt.</li> <li>31. exp Meta-Analysis/</li> <li>32. systematic review.mp.</li> </ol>

## Appendix 9: Excluded Final 27 Systematic Reviews and Reasons for Exclusion

Systematic review	Reason for exclusion
1. Bukkapatnam 2009 (Bukkapatnam et al., 2010)	Reports percentage of trial participants with prior CHD but not CVD
2. Chang 2013 (Chang et al., 2013)	Do not specify what percentage of trial participants are primary prevention
3. Chen 2012 (Chen et al., 2012)	Reports percentage of trial participants with prior CHD but not CVD
4. Chou 2016 (Chou et al., 2016)	Include studies in which the proportion of patients with prior CVD events is less than 10%
5. Corvol (Corvol et al., 2003)	Do not specify what percentage of trial participants are primary prevention
6. Costa (Costa et al., 2006)	Do not specify what percentage of trial participants are primary prevention
7. Danninger (Danninger et al., 2014)	Do not specify what percentage of trial participants are primary prevention
8. deVries (De Vries et al., 2012)	Do not specify what percentage of trial participants are primary prevention
9. Ijioma (Ijioma and Robinson, 2015)	Do not specify what percentage of trial are primary prevention trials. One included meta-analysis (Mora) differentiates exclusively primary prevention trials and predominantly primary prevention.
10. Kostis (Kostis et al., 2012)	Includes primary and secondary prevention trials.
11. Major (Major et al., 2015)	Do not specify what percentage of trial participants are primary prevention
12. Mills (Mills et al., 2008)	Includes primary and secondary prevention trials.
13. Naci (Naci et al., 2013a)	Do not specify what percentage of trial participants are primary prevention
14. Naci (Naci et al., 2013b)	Include studies in which the proportion of patients with prior CVD events is 20% or fewer
15. O'Regan (O'Regan et al., 2008)	Includes primary and secondary prevention trials.
16. Petretta (Petretta et al., 2010)	Do not specify what percentage of trial participants are primary prevention

17. Pignone (Pignone et al., 2000)	Do not specify what percentage of trial participants are primary prevention
18. Preiss (Preiss et al., 2015)	Do not specify what percentage of trial participants are primary prevention
19. Savarese (Savarese et al., 2013)	Do not specify what percentage of trial are primary prevention
20. Slinin (Slinin et al., 2012)	Includes only one exclusively primary prevention trial
21. Taylor (Hill-Taylor et al., 2013)	Do not specify what percentage of trial participants are primary prevention
22. Teng (Teng et al., 2015)	Includes only one exclusively primary prevention trial
23. Thavendirnathan (Thavendiranathan et al., 2006)	Include studies in which the proportion of patients with prior CVD events is up to 16.2%
24. Tonelli (Tonelli et al., 2011)	Do not specify what percentage of trial are primary prevention
25. Vijan (Vijan et al., 2004)	Include studies in which a proportion of patients had prior CVD events
26. Warshafsky (Warshafsky et al., 1999)	Do not specify what percentage of trial participants are primary prevention
27. Zhang (Zhang et al., 2014)	Do not specify what percentage of trial participants are primary prevention

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## **Appendix 10: Analyses from the Included Systematic Reviews that were not Included in Overview**

Mora et al. reported outcomes from three ‘exclusively primary prevention trials’ as well as from ‘predominantly or exclusively primary prevention trials’. I did not include outcomes reported in this SR from analyses of ‘predominantly or exclusively primary prevention trials’.

Some outcomes reported by CTT were results of analyses that included RCTs of more versus less statins and those that included secondary prevention participants and these were not eligible for the overview.

## Appendix 11: Interpretation of Composite Outcomes Reported in Included Systematic Reviews

Review	Composite outcome	Definition	Does the review describe proportion of each outcome comprises composite outcome?
CTT	Major coronary events	Non-fatal myocardial infarction or coronary death	No
	Major vascular events*	The first occurrence of any major coronary event, coronary revascularisation or stroke	No
Mora	Total CVD**	Predominantly myocardial infarction, angina/revascularization, stroke, and CVD death, with some of the trials including peripheral vascular events (AFCAPS & JUPITER) and 1 trial including ischemic congestive heart failure (AFCAPS).	
Ray	N/A	N/A	N/A

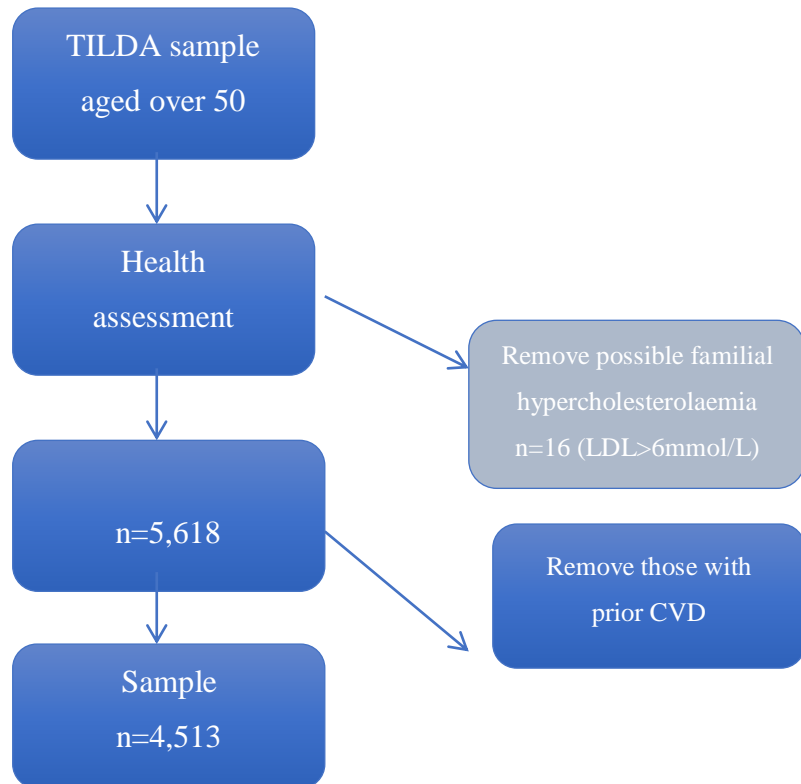
\* Abramson et al. (Should people at low risk of cardiovascular disease take a statin? BMJ 2013;347:f6123) noted that 35% the composite outcome ‘major vascular events’ comprised coronary revascularisations. This was calculated from Figure 1 of CTT 2012 by summing the number of events reported for ‘major coronary events’, ‘any stroke’ and ‘coronary revascularisation’ and calculating the proportion of this total sum that comprised ‘coronary revascularisation’. By this method we can calculate that ‘any stroke’ comprised 27% of the composite outcome and ‘major coronary events’ 38%. However, the outcome ‘major vascular events’ as reported in Figure 1 reported *first occurrences* major coronary event, coronary revascularisation or stroke and we cannot ascertain the proportion of each component of this outcome from the figure.

\*\* Mora et al. note that when the components of the composite outcome ‘total CVD’ in women are analysed in one large trial included in his analysis, women had a significant reduction in revascularisations and unstable angina but not in other components, including stroke, of the composite outcome.

## Appendix 12: Calculation of the Absolute Risk Benefit of Statins

Reduction in risk of CVD outcomes is presented in these reviews as relative risk reductions. However, for an individual patient, knowing their absolute risk reduction is more relevant when making a decision to take a statin. I used two theoretical patients to illustrate this point. One is a 65-year old man who smokes, does not have heart disease but who has high total cholesterol levels and elevated blood pressure. The second is a 45-year old woman who does not smoke, has elevated total cholesterol levels and slightly elevated blood pressure. Based on the ACC/AHA Risk calculator, the man has a 38% risk of having a major coronary event in the next ten years; the woman, a 1.4% risk. Risk reductions were reported by CTT stratified by baseline risk categories; (<5% risk RR 0.57 (CI 0.36 to 0.89);  $\geq 5\%$  to <10% risk RR 0.61 (CI 0.50 to 0.74);  $\geq 10\%$  to <20% risk RR 0.76 (CI 0.69 to 0.85);  $\geq 20\%$  to <30% risk RR 0.78 (CI 0.71 to 0.85);  $\geq 30\%$  risk RR 0.78 (CI 0.72 to 0.84)). According to those reported risk reductions, statin therapy would reduce the man's relative risk of major coronary events by 22% ( $\geq 30\%$  risk RR 0.78 (CI 0.72 to 0.84)) and the woman's relative risk by 43% (<5% risk RR 0.57 (CI 0.36 to 0.89)). However, the man could expect an *absolute* risk reduction of about 8.4% ( $38\% \times 0.22 = 8.4\%$ ) (Number Needed to Treat of 12); the woman by 0.6% ( $1.4\% \times 0.43 = 0.60\%$ ) (Number Needed to Treat of 166).

**Appendix 13: Flow Chart of the Number of Participants from The Irish Longitudinal Study on Ageing (TILDA) Included in the Analysis**



### Appendix 14: Thresholds of Risk Scores and Cholesterol Used to Assign Participants to Treatment Group

		1987	1994*	1998*	2004**	2007**	2012**	2016**
<b>Risk assessment</b>	<b>Patient characteristics</b>	N/A	≥20%	≥20%	≥5%	≥5%	< 1% ≥1 to<5% ≥ 5 to < 10% ≥10%	< 1% ≥1 to<5% ≥ 5 to < 10% ≥10%
<b>TC</b>	CVD	Treat if TC above 6.5mmol/l	Treat if TC over 8mmol/l Treat if under 8mmol/l but risk >20%	Treat if TC ≥ 5mmol/l	Treat if TC ≥ 4.5mmol/l	Treat if TC ≥ 4 mmol/l	N/A	N/A
	Diabetes			Treat if risk >20% & TC ≥ 5mmol/l	Treat if TC ≥ 4.5mmol/l	Treat if TC ≥ 4 mmol/l		
	Non-CVD/diabetes			Treat if risk >20% & TC ≥ 5mmol/l	Treat if risk ≥5% & TC ≥ 4.5mmol/l	Treat if risk ≥5% & TC ≥ 4 mmol/l		
<b>LDL</b>	CVD	N/A	N/A	Treat if LDL ≥ 3mmol/l	Treat if LDL ≥ 2.5mmol/l	Treat if LDL ≥ 2 mmol/l	Treat if LDL ≥ 1.8 mmol/l	Treat if LDL ≥ 1.8 mmol/l
	Diabetes			Treat if risk >20% & LDL ≥ 3mmol/l	Treat if LDL ≥ 2.5mmol/l	Treat if LDL ≥ 2 mmol/l	Treat if LDL ≥ 1.8 mmol/l	Treat if LDL ≥ 1.8 mmol/l
	Non-CVD/diabetes			Treat if risk >20% & LDL ≥ 3mmol/l	Treat if risk ≥5% & LDL ≥ 2.5mmol/l	Treat if risk ≥5% & LDL ≥ 2 mmol/l	Treat if risk ≥5% & LDL ≥ 1.8mmol/l Treat if risk ≥1 to<5% & LDL ≥ 2.5mmol/l Treat if risk < 1% & LDL ≥ 4.9mmol/l	Treat if risk ≥5% & LDL ≥ 1.8mmol/l Treat if risk ≥1 to<5% & LDL > 2.6mmol/l Treat if risk < 1% & LDL ≥ 4.9mmol/l

Notes: \* Coronary Risk Chart used for risk assessment. \*\* SCORE used for risk assessment. Abbreviations: TC = total cholesterol; LDL = low-density lipoprotein.

## **Appendix 15: Probabilistic Analysis of Cost Increases due to Widening Eligibility for Statins**

Uncertainty was explored using probabilistic methods, whereby a Monte Carlo simulation process was undertaken to generate 1,000 replications of the total cost estimates. This enabled the estimation of 95% confidence intervals for the total cost estimates. Firstly, input parameters for the proportion of the total over-50s population who did not have prior CVD and the proportions of the sample who would be eligible for statins under the various guidelines were assigned appropriate probability distributions. A deterministic unit cost was used, based on data provided by the PCRS. This was an average cost per person per year calculated from a sample month (June 2016) of types, costs and quantities of statins for the general medical services (GMS) scheme. The next stage of the probabilistic analysis was to propagate the uncertainty for all the input parameters through the model simultaneously. This process was undertaken using Monte Carlo simulation which re-runs the model a large number of times, with each simulation involving a random draw for a value from each of the input parameter distributions. The Monte Carlo simulation was set to 1,000 replications for the probabilistic analysis. The simulated results were then used to estimate 95% confidence intervals around the mean cost estimates. See Appendix 16.

## Appendix 16: Monte Carlo Simulation Results of Cost Increases due to Widening Eligibility for Statins

	<b>Guideline 1 1987</b>	<b>Guideline 2 1994</b>	<b>Guideline 3 1998</b>	<b>Guideline 4 2004</b>	<b>Guideline 5 2007</b>	<b>Guideline 6 2012</b>	<b>Guideline 7 2016</b>
<b>Total Cost</b>	€13,902,610	€16,924,365	€35,767,583	€58,256,655	€71,918,939	€108,959,843	€107,100,599
<b>MC Lower 95% CI</b>	€12,668,710	€15,364,265	€33,583,491	€55,808,914	€69,140,111	€106,127,604	€104,314,514
<b>MC Upper 95% CI</b>	€15,045,833	€18,456,889	€37,922,465	€60,866,411	€74,850,413	€112,017,290	€110,061,679
<b>Unit Cost</b>	149.33						
<b>Prevalence</b>	0.0795	0.0968	0.2046	0.3333	0.4114	0.6233	0.6127
<b>MC Lower 95% CI</b>	0.0730	0.0880	0.1928	0.3201	0.3960	0.6087	0.5983
<b>MC Upper 95% CI</b>	0.0858	0.1051	0.2170	0.3483	0.4262	0.6376	0.6274

Note: MC = Monte Carlo; CI = confidence interval.

## **Appendix 17: Conversion of 10-year Risk of Fatal CV Event (SCORE) to Comparable 10-year Risk of Fatal and Non-fatal CV Events (Coronary Risk Chart)**

I converted the risk of *fatal* CVD events (SCORE) to the comparable risk of *fatal and non-fatal* CVD events (Coronary Risk Chart) within the next ten years. Therefore <1%, 1% to <5%, 5% to <10% and  $\geq 10\%$  risk of fatal CVD events equate to <3%,  $\geq 3\%$  to <15%,  $\geq 15\%$  to <30% and  $\geq 30\%$  risk of fatal and non-fatal events.\*

\* 2012 ESC/EAS guidelines pg.1646 state “5% SCORE risk is equivalent of 15% total event rates from FINRISK - This three-fold multiplier is somewhat smaller in older persons in whom a first event is more likely to be fatal. An examination of the Framingham estimates of risk of total CVD events results in similar conclusions: a 5% SCORE risk of CVD death equates to a 10 – 25% Framingham risk of total CVD, depending upon which of the several Framingham functions is chosen.”

## Appendix 18: NNT to Prevent one Major Vascular Event in Lowest Risk Recommended Statins According to Each ESC/EAS Guideline

ESC/EAS guideline	Relative risk reduction in major vascular events from taking statins*	Lowest level of baseline risk for which statins could be recommended	Equivalent five year baseline risk of fatal and non-fatal CVD events**	NNT
1987	0.75 (0.70 – 0.80)	Not defined	Not applicable	Not applicable
1994	0.75 (0.70 – 0.80)	20% Coronary Risk Chart	10%	40
1997	0.75 (0.70 – 0.80)	20% Coronary Risk Chart	10%	40
2004	0.75 (0.70 – 0.80)	5% SCORE	7.5%	73
2007	0.75 (0.70 – 0.80)	5% SCORE	7.5%	73
2012	0.75 (0.70 – 0.80)	1% SCORE	3%	400
2016	0.75 (0.70 – 0.80)	1% SCORE	3%	400

Note: \* RR reported for the outcome ‘Major Vascular Events’ as reported in Cholesterol Treatment Trialists C, Fulcher J, O’Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397-405. \*\* See Appendices 17 and 20.

**Appendix 19: NNT to Prevent one Major Vascular Event in Those Classified as Low, Medium, High and Very-high Risk by the 2016 ESC/EAS Guidelines**

<b>Absolute five-year risk of fatal and non-fatal CVD events*</b>	<b>Relative risk reduction in major vascular events from taking statins (RR)**</b>	<b>Absolute risk reduction of major vascular events from taking statins</b>	<b>NNT</b>
<b>Low-risk</b> <1%	0.75 (0.70 – 0.80)	<0.25%	400 or more
<b>Moderate risk</b> ≥1% to <7.5%	0.75 (0.70 – 0.80)	≥0.25% to <1.9%	400 to 53
<b>High risk</b> ≥7.5% to < 16%	0.75 (0.70 – 0.80)	≥1.9% to <4%	53 to 25
<b>Very high risk</b> ≥16%	0.75 (0.70 – 0.80)	≥4%	25 or less

Notes: \* See Appendices 17 and 20. \*\* RR reported for the outcome ‘Major Vascular Events’ as reported in Cholesterol Treatment Trialists C, Fulcher J, O’Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397-405.

## **Appendix 20: Conversion of 10-year Risk of Fatal and Non-fatal CV Events to Five-year Risk of Fatal and Non-fatal CV Events**

I converted each profiles' ten-year risk to five-year risk. Therefore <3%, ≥3% to <15%, ≥15% to <30% and ≥30% risk of fatal and non-fatal events equate to <1%, ≥1% to <7.5%, ≥7.5% to < 16% and ≥16% risk of fatal and non-fatal events.\*\*

\*\* Mc Cormack "Primary prevention of heart disease and stroke: a simplified approach to estimating risk of events and making drug treatment choices" CMAJ 1997 compare five and ten year risk of cardiovascular event (Figure 1). This is based on material from Anderson et al. "An updated coronary risk profile: a statement for health professionals." Circulation 1991; 83:356-62 and was based on a Framingham risk model equation.

## Appendix 21: Calculation of the Proportion of Statin-eligible Patients, According to Each Guideline, Who Reach an NNT ≤ 30

Using Stata 13.1, I estimated the baseline risk for each TILDA participant and the proportion of those who would be eligible for statin therapy according to each guideline. An NNT = 30 is the inverse of an absolute risk reduction of 3.33%. I assumed that taking statins reduced a person's risk of 'major vascular events' by 25% ((RR 0.75 (CI 0.70-0.80) as reported in a systematic review\* and meta-analysis of primary prevention trials only) and that the RR was consistent across all groups. I then estimated the baseline level of risk a person would have to have to achieve an absolute risk reduction of 3.33% given the relative risk reduction from taking statins is 25%. In terms of the SCORE risk assessment method, a person with a baseline risk of 8.3% would achieve an absolute risk reduction of 3.33%. (See below). I then cross tabulated those eligible for statins, according to each guideline, with those at and above a baseline risk of 8.3%.

NNT = 30 = ARR = 1/30 = 0.033 (3.33%)
RR reduction = 0.25
0.033 x 4 = 13.2% 5-year baseline risk of fatal and non-fatal CV event
Covert 5-year baseline risk of fatal and non-fatal CV event to 10-year baseline risk of fatal CV event (See Appendices 4 and 7)
13.2% 5-year baseline risk of fatal and non-fatal CV event is equivalent of 8.3% 10-year baseline risk of fatal CV event

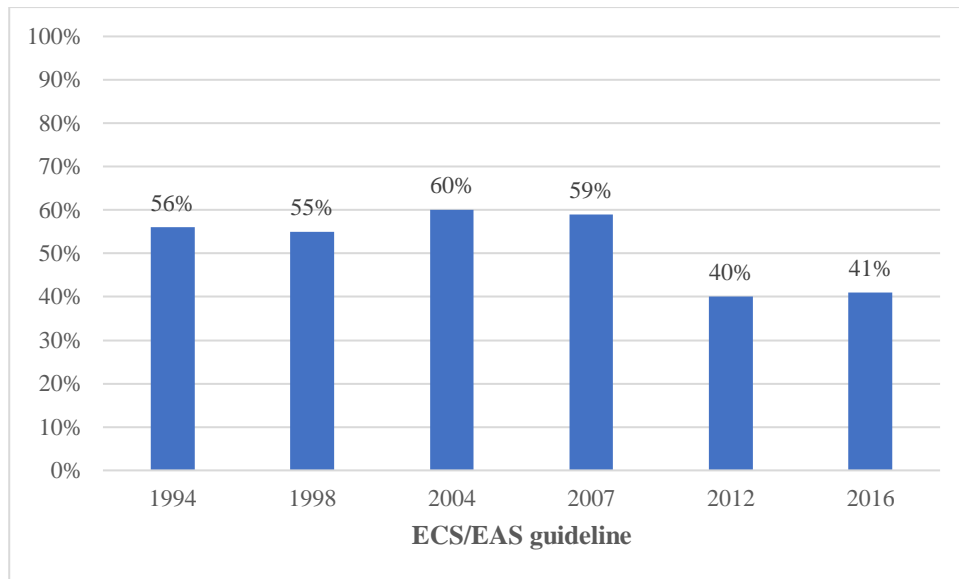
Note: \* Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes E, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-90.

**Appendix 22: Proportion of Those Eligible for Statins According to Each ESC/EAS Guideline who would Consider Taking a Medication with an  $NNT \leq 30$**

<b>Guideline year</b>	<b>Proportion of those eligible for statins whose <math>NNT \leq 30</math> (%)</b>	<b>Proportion of those eligible for statins who accept <math>NNT \leq 30</math> (minimum 46%)*</b>	<b>Proportion of those eligible for statins who accept <math>NNT \leq 30</math> (average 71%)*</b>	<b>Proportion of those eligible for statins who accept <math>NNT \leq 30</math> (maximum 87%)*</b>
1994	79	36	56	69
1998	77	35	55	67
2004	84	39	60	73
2007	83	38	59	72
2012	57	26	40	50
2016	58	27	41	50

Note: \*Albarqouni report that between 46% and 87% (average 71%) of participants would consider taking a medication with an  $NNT \leq 30$ .

## Appendix 23: Proportion of those Eligible for Statins who Accept their NNT



Note: I assume that no participant whose  $NNT > 30$  accept taking statins.

## Appendix 24: Excluded Final 24 Articles and Reasons for Exclusion

Author	Reason for exclusion	Year
1. Carey	No, secondary prevention	2012
2. Carrington	No, concerns adherence, no patient/doctor views	2009
3. Casebeer	No, concerns adherence, no patient/doctor views	2009
4. Chaudhry	No quantitative analysis of adherence	2008
5. Cheetham	No, concerns adherence, no patient/doctor views	2013
6. de Ferranti	No, paediatrics	2017
7. Dormuth	No, describes bias in studies (relationship between statins and accidents)	2009
8. Garavalia	No, secondary prevention	2009
9. Jackevious	No, quantitative analysis of adherence	2002
10. Johal	No, concerns statin users adhering to healthy lifestyle and diet	2017
11. Karner	No, secondary prevention	2002
12. Kalia	No, impact of calcium score on adherence	2015
13. Latry	No, quant analysis of adherence versus risk factors	2011
14. Lehane	No, secondary prevention	2008
15. Lewis	No, opinion on guidelines and compliance	2010
16. Ma	No, not statins, other medications too	2015
17. Nanchen	No, about an interactive decision aid	2015
18. Nieuwkerk	No, effect of an intervention	2012
19. Senior	No, familial hypercholesterolaemia	2007
20. Simons	No, quantitative analysis of adherence	2011
21. Slejko	No, secondary prevention	2014
22. Speechly	No, secondary prevention	2010
23. Tvaryanas	No, quantitative analysis only	2017
24. Yilmaz	No, secondary prevention	2005

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## Appendix 25: Included Articles

Author	Focus	Year
1. Ab	Interviews with doctors	2008
2. Bonner	Interviews with doctors	2015
3. Durack-Brown	Interviews with patients and doctors	2003
4. Fung	Focus groups with patients	2010
5. Gialamas	Telephone interviews with patients	2011
6. Jansen	Interviews with doctors	2017
7. Jovanovic	Interviews with female patients	2014
8. Ju	Systematic review of qualitative studies regarding patients	2017
9. Kedward	Interviews with doctors	2003
10. Kirkegaard	Interviews with patients	2013
11. Kruger	Interviews with doctors	2018
12. Nixon	Interviews with doctors	2016
13. Polak 2016 1	Interviews with patients	2016
14. Polak 2016 2	Interviews with patients	2016
15. Saukko	Interviews with patients	2011
16. Silwer	Interviews with doctors	2010
17. Tolmie	Interviews with patients	2003
18. Turner	Interviews with patients	2013
19. Will 2013	Interviews with patients	2013

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