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Familial Hypercholesterolaemia: three decades of advances in therapy

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FAMILIAL HYPERCHOLESTEROLAEMIA
– THREE DECADES OF ADVANCES IN THERAPY

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Original published work submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa in fulfilment of the requirements for the Degree
of
Doctor of Science in Medicine

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PREFACE

In this thesis original published works are presented in fulfillment of the requirements for the degree of Doctor of Science in Medicine, of the University of the Witwatersrand. All papers have been published in peer-reviewed journals which are fully indexed internationally.

1. Organizational Methodology

The thesis is written according to the "Style Guide for Theses, Dissertations and Research Reports" of the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. All references are cited in the Vancouver style. In the introduction to the thesis all publications included in the thesis are listed. However, for ease of reference, in the main body of the thesis the candidate's published works are grouped together in themes and topics for each chapter, and are appended at the end of each chapter.

2. Prizes and Awards

A number of the publications have been presented in abstract form at both local and international congresses and several have been awarded prizes. The details of the awards are as follows:

a. **Publication 3** (Paiker JE, Raal FJ, Waisberg R, Buthelezi EP. Quantity versus quality of LDL cholesterol in patients with familial hypercholesterolaemia - which is more important? Clinica Chimica Acta 2001;314:167-173) and **publication 26** (Raal FJ, Scott R, Somaratne R, Bridges I, Li G, Wasserman SM and Stein EA. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal

antibody to proprotein convertase subtilisin/kexin type 9 serine protease, in patients with heterozygous familial hypercholesterolemia. The reduction of LDL-C with PSCK9 inhibition in heterozygous familial hypercholesterolemia disorder (RUTHERFORD) randomized trial. Circulation 2012;126:2408-2417) were both awarded the AstraZeneca publication award for the best papers published in the field of Lipidology in South Africa in 2002 and 2013, respectively.

b. A poster presentation of **publication 35** (Raal FJ, Honarpour N, Blom D, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): Results of a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:341-50) was awarded the Best Poster Award at the 82nd European Atherosclerosis Society Congress, May 31st - 3rd June, 2014, Madrid, Spain.

c. An abstract of **publication 50** (Ginsberg HN, Tuomilehto, Hovingh GK, Cariou B, Santos RD, Brown AS, Sanganalmath SK, Koren A, Thompson D, Raal FJ. Impact of age on the efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia. Cardiovascular Drugs and Therapy. 2019;33:69-76) was awarded a certificate, by the American College of Cardiology at the ACC meeting held in Chicago in April 2016, for the highest ranking abstract submitted from South Africa.

d. **Publication 55** (Raal FJ, Kallend D, Ray KK, Turner T, Koenig W, Wright RS, Wijngaard PLJ, Curcio D, Jaros MJ, Leiter LA, Kastelein JJP. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med

2020;382:1520-1530) was awarded Paper of the Year for 2020, late discovery category, by the Oligonucleotide Therapeutics Society.

e. An abstract of **publication 62** (Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, Ali S, Banerjee P, Chan K-C, Gipe DA, Khilla N, Pordy R, Weinreich DM, Yancopoulos GD, Zhang Y, Gaudet D. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med 2020;383:711-720) was awarded the Paul Dudley White International Scholar Award for the highest ranked abstract from South Africa, at the American Heart Association Scientific Sessions 2020.

DECLARATION

I, Frederick Johan Raal, do hereby declare that the published works submitted by me for the degree of Doctor of Science in Medicine represent work carried out by me or in which I have actively participated. This thesis is a collection of my publications over the past three decades related to the diagnosis, management and advances in therapy of familial hypercholesterolaemia. Overall, there are 113 publications included in this thesis, of which I am either first or senior author (First author 32; Senior author 27).
For publications in which I am not first author, I have received permission from the primary author to use the publication for the purpose of this thesis.

The publications in this thesis include:

1. Work carried out largely by me, in which I contributed substantially to the design of the studies, evaluation of the results and preparation of the manuscripts, together with collaborators (publications 5,7,12,15,17,18,21,22,23,26,27,34,35,41,50,52,53,55,59, 62,73,79,81,82,84,87,94,97,102,110,111,112).

2. Work that was shared equally with collaborators (publications 1,2,3,8,9,10,11,13,16, 19,20,24,25,28,29,30,31,32,33,36,37,38,39,40,42,43,44,45,46,47,48,49,51,54,56, 57,58,60,61,63,64,65,66,67,68,69,70,71,72,74,77,78,80,83,85,86,88,89,90,91,92, 93,95,96,98,99,100,101,103,104,105,106,107,108,109,113).

3. Work carried out by higher degree candidates. My contribution was to help plan the projects and to assist with evaluation of results and preparation of the findings for publication. This work was included in three MMed degrees (publications 4,6 and 14) and two PhDs (publications 75 and 76) all at the University of the Witwatersrand.

4. All the work represented in this thesis was carried out in the Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

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Frederick Johan Raal

DEDICATION

To my wonderful family, my wife Anne and two children Philippa and Nicholas, for their never-ending support, love and understanding throughout my career and life.

ABSTRACT

Severe familial hypercholesterolaemia (FH), particularly homozygous FH (HoFH), remains a difficult condition to treat. As a result of markedly elevated low density lipoprotein-cholesterol (LDL-C) levels from conception, subjects with severe FH suffer from accelerated, premature atherosclerotic cardiovascular disease often resulting in premature death. However, there have been remarkable advances in treatment for this condition and this thesis describes the advances in therapy for FH over the past three decades. Lipid lowering therapies which act mainly by up regulating LDL receptor (LDLR) function, such as high intensity statin, ezetimibe and PCSK9-inhibitors, form the backbone of treatment. This combination is often sufficient to attain LDL-C targets in the majority of subject with heterozygous FH (HeFH). However, a small percentage of HeFH and the vast majority of HoFH patients are unable to achieve acceptable LDL-C levels even with this combination therapy. The addition of therapies that are independent of LDLR function, such as lomitapide and, more recently, the ANGPTL3 inhibitor, evinacumab, are required. These therapies have reduced the need for lipoprotein apheresis which is now only required for the most severe cases, particularly for those HoFH patients with minimal or no residual LDLR function. Prospects for gene therapy are promising. However, despite substantial progress, several technical issues still need to be resolved before this therapy can be safely and effectively applied.

Overcoming the challenges of severe FH has been a long and difficult journey, but with the treatment options now available, the future for severe FH looks bright.

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I hereby wish to acknowledge:

- My research staff and both local, national, and international collaborators who I have had the pleasure of dealing with throughout my academic career.

- Most especially my patients, particularly my patients with homozygous familial hypercholesterolaemia, who have participated willingly in multiple studies over the years. It has been a wonderful experience for me to observe my FH patients, many of whom I have treated from a very young age and for over 30 years, mature and grow up. It has been very rewarding to observe their gratitude and their joy as their LDL-cholesterol levels have been lowered further and further with novel therapies.

- The staff of the Faculty of Health Sciences at the University of the Witwatersrand who have encouraged and supported my research over three decades.

ABBREVIATIONS

ACAT	Acyl-coA cholesterol acyltransferase
ANGPTL3	Angiopoietin-like protein 3
apoB	apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
CETP	Cholesteryl ester transfer protein
CRP	C-reactive protein
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FH	Familial hypercholesterolaemia
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
LASSA	Lipid and Atherosclerosis Society of Southern Africa
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LLRx	Lipid lowering therapy
LDLR	Low density lipoprotein receptor
mAb	monoclonal antibody
PCSK9	Proprotein convertase subtilisin kexin 9
siRNA	small interfering ribonucleic acid
T-C	Total cholesterol
VLDL	Very low density lipoprotein

LIST OF PUBLICATIONS INCLUDED IN THIS THESIS

1. Paiker JE, Raal FJ, von Arb M. Auto-antibodies against oxidised LDL as a marker of coronary artery disease in patients with familial hypercholesterolaemia. Ann Clin Biochem 2000;37:174-178.
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CHAPTER 1: INTRODUCTION

My main area of research interest has been in subjects with familial hypercholesterolaemia (FH). FH is one of the most common inherited disorders in the world affecting approximately 1 in every 300 persons, or over 30 million people, worldwide. In the Afrikaner, Jewish and Indian populations of South Africa the prevalence is even higher, with about 1 in every 80 persons affected. FH is mainly caused by mutations affecting the function of the LDLR which lead to diminished clearance of cholesterol from the circulation and, consequently, to markedly elevated LDL-C levels. Less frequently FH can result from mutations in apoB or gain-of-function mutations in PCSK9. The resultant hypercholesterolaemia predisposes these patients to severe premature atherosclerosis, particularly atherosclerotic coronary artery disease. The concentration of LDL-C and lifetime vascular exposure to raised plasma LDL-C concentrations are major determinants of atherosclerosis, but there remains a considerable variability in the extent of atherosclerosis present and in the expression of atherosclerotic cardiovascular disease (ASCVD) in these patients. Other genetic or environmental factors affecting LDLR function or qualitative differences in LDL, such as LDL particle size and susceptibility to lipid oxidation, may play a role, as may other biochemical risk factors.

Initial treatment of homozygous FH (HoFH) included oral therapy with the bile-acid sequestrant cholestyramine, which was poorly tolerated and of limited efficacy. Portacaval shunt or ileal bypass surgery was also performed but these surgical procedures were shown to be of limited, if any, benefit. The role of lipid oxidation in the pathogenesis of atherosclerosis became a major focus of lipid research in the 1990s, the hypothesis being that antioxidants may slow progression or even reverse atherosclerosis. At the time, we initiated studies with probucol, a potent antioxidant, as well as with high doses of vitamin E, a fat-soluble antioxidant, in subjects with HoFH. However, antioxidants were shown to be of little benefit in this patient group.

The purpose of my PhD thesis, which I was awarded in 1999, was to determine whether such qualitative differences in LDL are important determinants of the extent and severity of atherosclerosis and to determine whether it is mainly the reduction in LDL-C that is of benefit, or whether antioxidant therapy would also be effective in preventing progression of atherosclerosis in FH subjects. FH patients, particularly patients with HoFH were found to have large, buoyant LDL particles, which are less susceptible to lipid oxidation than smaller,

denser particles. Interestingly, in the absence of other causes of insulin resistance, patients with FH have normal fasting insulin and triglyceride levels, normal postprandial lipaemia, and do not have microalbuminuria (1.1; publications 1-8). They, therefore, usually show no features of the metabolic syndrome despite severe, accelerated atherosclerosis. The conclusion of my thesis was that in subjects with FH, quantitative rather than qualitative differences in LDL are associated with accelerated atherosclerosis and that therapy in FH should therefore be aimed primarily at reducing LDL-C bulk by reducing the LDL-C level as early and as aggressively as possible (1.1; publications 5,7. 1.2; publication 1). Publications included in my PhD thesis and therefore not included in this thesis are listed below (1.1; publications 1-8). Additional publications in this area not included in my PhD thesis and forming part of this thesis are also shown (1.2; publications 1-4).

Publications

1.1 Part of PhD so referenced but not included in this thesis

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2. Areias AJ, Richardson J, Raal FJ. Rapid method for measuring copper induced LDL oxidation. Eur J Lab Med 1995;1:95-97.
3. Zouvanis M, Raal FJ, Joffe BI, Seftel HC. Microalbuminuria is not associated with cardiovascular disease in patients with homozygous familial hypercholesterolaemia. Atherosclerosis 1995;113:289-292.
4. Raal FJ, Areias AJ, Waisberg R, von Arb M. Susceptibility of low density lipoprotein to oxidation in familial hypercholesterolaemia. Atherosclerosis 1995;115:9-15.
5. Raal FJ, Areias AJ, Joffe BI. Low density lipoproteins and atherosclerosis - quantity or quality? Redox Report 1995;1:171-176.
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8. Raal FJ, Pilcher GJ, Veller MG, Kotze MJ, Joffe BI. Efficacy of vitamin E compared to either simvastatin or atorvastatin in preventing the progression of atherosclerosis in homozygous familial hypercholesterolemia. Am J Cardiol 1999;84:1344-1346.

1.2 Additional publications in this area forming part of this thesis

1. Paiker JE, Raal FJ, Waisberg R, Buthelezi EP. Quantity versus quality of LDL cholesterol in patients with familial hypercholesterolaemia –which is more important? Clinica Chimica Acta 2001;314:167-173.
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3. Paiker J, Raal FJ, Veller M, von Arb M, Chetty N, Naran NH. Cell adhesion molecules - can they be used to predict coronary artery disease in patients with familial hypercholesterolaemia? Clin Chimica Acta 2000;293:105-113.
4. Zamparini J, Immelman AR, Raal FJ. Fibroblast Growth Factor-23 in patients with homozygous familial hypercholesterolaemia. J Clin Lipidology 2018;12:767-772.

CHAPTER 2: THE STATIN AND EZETIMIBE ERA

With the arrival of statin therapy in South Africa in the late 1990s, and with the lack of efficacy of antioxidant therapy in HoFH subjects, my research focus changed. Therapy aimed primarily at reducing LDL-C levels as early and as aggressively as possible became paramount. I have shown, in collaboration with many local and international colleagues, that high dose statin therapy can reduce LDL-C levels in subjects with HoFH, even in those who are receptor negative - suggesting that high dose statin therapy must also act, at least in part, by reducing or inhibiting very low density lipoprotein (VLDL) and apolipoprotein B (apoB) production (2.1; publications 1,2. 2.2; publications 1-6). More recently another proposed mechanism has been statin induced hepatic retinoid X receptor activation with reduction in ANGPTL3 levels. Resins are poorly tolerated but the introduction of resins that were better tolerated, such as colesevelam and the cholesterol absorption inhibitor, ezetimibe, shortly after statins were introduced allowed for a further reduction in LDL-C levels even in subjects with HoFH (2.2; publications 7-9). In resource poor countries like South Africa where access to lipoprotein apheresis is not readily available or affordable, we have shown that high intensity statin plus ezetimibe therapy reintroduced in the second trimester of pregnancy once the foetus is fully formed, appears to be safe (2.2; publication 10).

2. Publications

2.1 Part of PhD so referenced but not included in this Thesis

1. Raal FJ, Pilcher GJ, Illingworth DR, Pappu AS, Stein EA, Laskarzewski P, Mitchel YB, Melino MR. Expanded-dose simvastatin is effective in homozygous familial hypercholesterolaemia. Atherosclerosis 1997;135:249-256.
2. Raal FJ, Pappu AS, Illingworth DR, Pilcher GJ, Marais AD, Firth JC, Heinonen TM, Black DM. Inhibition of cholesterol synthesis by atorvastatin in homozygous familial hypercholesterolaemia. Atherosclerosis 2000;150:421-428.

2.2 Additional publications in this area forming part of this Thesis

1. **Raal FJ**, Pilcher G, Rubinsztein DC, Lingenhel A, Utermann G. Statin therapy in a kindred with both apolipoprotein-B and low density lipoprotein receptor gene defects. Atherosclerosis 1997;129:97-102.
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3. **Raal FJ.** A single centre retrospective observational study to evaluate the change in total cholesterol and LDL-cholesterol in hyperlipidaemic patients switched from atorvastatin to simvastatin. Cardiovasc J South Afr 2004;15:118-123.
4. Marais AD, Raal FJ, Stein EA, Rader DJ, Blasetto J, Watkins C, Palmer M, Wilpshaar W. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis 2008;197:400-406.
5. Panz V, Immelman A, Paiker J, Pilcher G and Raal FJ. High-dose statin therapy does not induce insulin resistance in patients with familial hypercholesterolemia. Metabolic Syndrome and Related Disorders 2012;10:1-7.
6. Stein EA, Dann EJ, Weigman A, Skovby F, Gaudet D, Sokal E, Charng M-J, Mohamed M, Luirink I, Raichlen JS, Sunden M, Carlsson SC, Raal FJ, Kastelein JJP. Efficacy of rosuvastatin in children with homozygous familial hypercholesterolemia and association with underlying genetic mutations. J Am Coll Cardiol 2017;70:1162-70.
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9. Stein EA, Marais AD, Szamosi T, Raal FJ, et al. Colesevelam hydrochloride: Efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. J Pediatric 2010;156:231-6.

10. Botha TC, Pilcher GJ, Wolmarans K, Blom DJ, Raal FJ. Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia – a retrospective review of 39 pregnancies. Atherosclerosis 2018;277:502-507.

CHAPTER 3: MIPOMERSEN, LOMITAPIDE AND SOME FAILED THERAPIES FOR SEVERE FH

However, despite high-intensity statin together with ezetimibe therapy, severe FH patients, especially those with HoFH, are unable to achieve acceptable LDL-C levels. New therapies that would lower LDL-C further were needed. I was involved in studies with novel agents such as ACAT inhibitors (3; publications 1-3), CETP inhibitors, and thyromimetics in this patient group but none of these therapies stood the test of time and were discontinued because of lack of efficacy or safety reasons. I reported in the Lancet on the use of mipomersen, a novel antisense oligonucleotide directed against apoB, in HoFH subjects (3; publication 4). Twenty-six of the 51 subjects enrolled into this study were my patients. Mipomersen was shown to be effective and reduced LDL-C by a further 30% and also lowered Lp(a) levels by 25% in HoFH patients (3; publications 4-8). Unfortunately, because of side effects, this therapy has also been withdrawn from the market. Lomitapide, the microsomal triglyceride transfer protein (MTP) inhibitor, is however still an option for patients with severe HoFH but the concern is hepatic steatosis (3; publications 9-11)

3. Publications

1. **Raal FJ**, Marais AD, Lovalvo J, Klepack E, McLain R, Heinonen T. Avasimibe, an ACAT inhibitor, enhances the lipid lowering effect of atorvastatin in subjects with homozygous familial hypercholesterolemia. Atherosclerosis 2003;171:273-279.
2. Kastelein JJP, van Leuven SI, Burgess L, for the Radiance Investigators. Effect of Torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Engl J Med 2007;356:1620-1630.
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5. Santos R, Raal FJ, Donovan J and Cromwell W. Mipomersen preferentially reduces small LDL particle number in patients with hypercholesterolemia. Journal of Clinical Lipidology 2015;9:201-9.
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CHAPTER 4: PCSK9 INHIBITION, MONOCLONAL ANTIBODIES AND INCLISIRAN

The management of HeFH has been revolutionized by the introduction of PCSK9-inhibitors. Together with high-intensity statin, with or without ezetimibe therapy, these agents reduce LDL-C a further 60% allowing many patients with HeFH to achieve LDL-C levels we were not able to achieve previously (4; publications 1-26). This therapy also modestly reduces Lp(a) by approximately 30% (4; publications 27-29). PCSK9-inhibitor therapy has also been shown to reduce cardiovascular events in large outcome studies in subjects with established ASCVD or at high risk for ASCVD (4; publications 11,12). As PCSK9-inhibitors act indirectly by up-regulating LDLR function it was uncertain whether these drugs would work in subjects with HoFH who may have minimal or no residual LDLR function. However, the vast majority, over 70%, of HoFH patients, identified worldwide are receptor “defective" rather than receptor negative and have some residual LDLR activity which could be upregulated by PCSK9-inhibitor therapy. I drew the attention of the pharmaceutical industry to this unmet need and approached two companies who were leading the development of PCSK9-inhibitor therapy with mAbs at the time. Amgen kindly agreed to the proposal provided I helped with the study design. Two Investigator initiated studies were performed. The first study was a proof-of-concept study in 8 HoFH subjects which demonstrated that PCSK9-inhibitor therapy is indeed effective in HoFH (4; publication 6). This was published in *Circulation* in 2013. Subsequently a much larger, double-blind, placebo-controlled study with the PCSK9-inhibitor, evolocumab, was performed. In 2015, I published two articles in the same edition of *the Lancet* on the safety and efficacy of the PCSK9 mAb inhibitor evolocumab in subjects with either HeFH (RUTHERFORD study) or HoFH (TESLA study) (4; publications 9,10). Used in combination with other lipid-lowering therapies, this therapy reduced LDL-C by a further 60% in HeFH subjects and by a further 30% in those with HoFH. In these papers, I also reported on the effect the underlying FH genotype has on response to PCSK9 mAb inhibitor therapy. The underlying genotype does not affect the response in subjects with HeFH probably because of marked upregulation of the 50% normal LDL receptors but in those with HoFH the response is determined by the underlying genotype (4, publication 9). Those HoFH patients with residual LDL receptor activity (non-null) respond well but those with minimal or no residual LDL receptor activity (null/null) respond poorly, if at all, to this therapy (4; publications 10,16,19). These two papers have been widely cited and this therapy has revolutionised the management of severe FH.

Rather than inhibiting PCSK9 with mAb therapy, inhibiting the production of PCSK9 by the liver by means of small interfering RNA (siRNA), is also a revolutionary approach (4; publications 30-36). This therapy has been shown to similarly reduce LDL-C by a further 50%. As first author I recently published the results of treatment with inclisiran, a siRNA directly against PCSK9, in subjects with HeFH, in the *New England Journal of Medicine* in 2020 (4; publication 30). A pilot study showed that inclisiran may also be effective at least in some subjects with HoFH (4; publication 32). The advantage over mAb therapy is that inclisiran only needs to be administered twice a year which will revolutionize the management of difficult-to-treat hypercholesterolaemia and guarantee compliance.

4. Publications

1. **Raal FJ**, Scott R, Somaratne R, Bridges I, Li G, Wasserman SM and Stein EA. Low-Density Lipoprotein Cholesterol-Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients with Heterozygous Familial Hypercholesterolemia. The reduction of LDL-C with PSCK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial. Circulation 2012;126:2408-2417.
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CHAPTER 5: ANGPTL3 INHIBITION

Despite high-intensity statin, ezetimibe, as well as PCSK9-inhibitor therapy, HoFH patients are unable to achieve acceptable LDL-C levels and often require LDL apheresis. As first author I recently published the results of a study with the ANGPTL3-inhibitor, evinacumab, in HoFH patients, also published in the *New England Journal of Medicine* (5; publication 1). This remarkable therapy which is given as a monthly intravenous infusion was shown to reduce LDL-C by a further 50% and the effect was independent of LDL receptor function so is equally effective in those HoFH patients with minimal or no residual LDL receptor function (null/null HoFH). For the first time the addition of this therapy will allow many of our HoFH patients to achieve near normal LDL-C levels. These novel therapies have reduced the need for lipoprotein apheresis or liver transplantation which is now only required for the most severe cases. Perhaps in the future, gene therapy for HoFH may also become a reality. Over the past three decades it has been heartwarming to witness how HoFH has been converted from a condition that was often fatal in childhood to a manageable dyslipidaemia which has extended the lives of these unfortunate patients and improved their quality of life (5; publication 2,3).

5. Publications

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CHAPTER 6: FH IN SOUTH AFRICA

With my interest in FH spanning more than three decades, and in collaboration with many local, national and international colleagues, I have described the clinical presentation, genetics and prevalence of FH, both HeFH and HoFH, in all population groups in South Africa (6; publications 1-9). However, our knowledge about the prevalence of FH in black Africans remains rudimentary and requires further study, as very few black Africans have been diagnosed with FH and even less are being treated (6; publications 10-12). This is an important area of my ongoing and future research. Together with Hans-Georg Kraft and Gert Utermann, I was also the first to report high Lp(a) levels in patients with both HeFH and HoFH (6; publication 13).

6. Publications

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CHAPTER 7: LOCAL AND INTERNATIONAL FH AND LIPID GUIDELINES

I have been Chairperson and Secretary of the Society of Endocrinology, Metabolism and Diabetes of Southern Africa (SEMDSA) and have also been Secretary of the Lipid and Atherosclerosis Society of Southern Africa (LASSA) since its inception in 1989. In this capacity I have been intimately involved in the development and distribution of South African guidelines for the awareness and management of both FH as well as hyperlipidaemia in general (7; publications 1-15).

Progress in this area is not only important for our patients with HoFH and severe HeFH, but for all patients with FH, one of the commonest inherited disorders worldwide. In 2013, I acted on an expert panel to produce a paper which highlighted the extent to which FH is underdiagnosed and undertreated in the general population. We estimated that there are between 20 and 34 million individuals worldwide with FH and at least 120 000 individuals in South Africa (7; publication 16). As the condition is asymptomatic it is often missed and it is estimated that less than 5% individuals affected with HeFH are diagnosed worldwide. The article discussed recommendations on how to better diagnose and treat individuals and families with FH and to ultimately prevent premature coronary heart disease. This paper also highlighted the urgent worldwide need for diagnostic screening and timely and aggressive treatment of the condition in these high risk individuals. I have also co-authored Consensus Statements on the diagnosis and treatment of both HeFH and HoFH published in the European Heart Journal as well as other International FH guidelines. I have also been on the EAS Consensus Panel for Consensus Statements on statin associated muscle symptoms as well as the management of FH in children and adolescents (7; publications 16-27). I am on the Steering Committee developing a worldwide registry of HeFH and HoFH subjects which aims to assist with identification of undiagnosed FH subjects and to allow them to benefit from the remarkable novel therapies under development for this condition (7; publications 28-30). More recently, with the arrival of the coronavirus disease 2019 (COVID-19) pandemic, I have co-authored several manuscripts on the risk and importance of ongoing lipid-lowering therapy in FH patients who become infected with COVID-19 (7; publications 31,32).

I have also been asked to do several reviews on novel therapies for severe FH and continue to do so. This research, in which I have been intimately involved in both planning of study concepts and design, has been very rewarding to me and particularly to my FH patients. With these novel therapies in advanced stages of development, in which I have played a pivotal

role, it will be possible to effectively treat the hypercholesterolaemia in virtually all HeFH patients and a large percentage of HoFH patients. This will allow these patients to live healthier, longer lives.

7. Publications

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CHAPTER 8: REDUCTION IN MORTALITY IN SEVERE FH

Prior to statins HoFH patients rarely survived beyond the age of 20 years. The pivotal high dose statin studies we conducted with simvastatin, atorvastatin and rosuvastatin confirmed the efficacy of high intensity statin therapy in this patient group. Although ideal LDL-C levels are not achieved with the use of high dose statins, cardiovascular morbidity and mortality have definitely been reduced and life expectancy has been prolonged (8; publications 1-4). I was the first to describe the long-term cardiovascular benefit of lipid-lowering therapy in the largest cohort of HoFH patients reported at the time (8; publication 1). With the newer therapies and novel therapies under development hopefully morbidity and mortality from FH will be reduced even further.

8. Publications

1. **Raal FJ**, Pilcher GJ, Panz VR et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation 2011;124:2202-2207.
2. **Raal FJ**, Sjouke B, Hovingh GK, Isaac BF. Phenotype diversity among patients with homozygous familial hypercholesterolemia: A cohort study. Atherosclerosis 2016;248:238-44.
3. **Raal FJ**, Sjouke B, Hovingh GK, Isaac BF. Retrospective analysis of cohort database: Phenotypic variability in a large dataset of patients confirmed to have homozygous familial hypercholesterolemia. Data in Brief 2016;7:1458-62.
4. Thompson GR, Blom DJ, Marais AD, Seed M, Pilcher GJ, Raal FJ. Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. European Heart Journal 2018;39:1162-1168.

CHAPTER 9: CONCLUSIONS AND PLANNED FUTURE RESEARCH

A major focus of my research remains the clinical, biochemical, genetic and therapeutic management of FH. I continue to conduct studies with novel therapies such as the adnectin LIB003, a novel PCSK9-inhibitor therapy, as well as ANGPTL3-inhibitor therapy, evinacumab, in this patient group. These therapies have had a major impact on the lives of FH patients, particularly those with HoFH. It has been a wonderful experience for me to observe my HoFH patients, many of whom I have been treating from a very young age and for over 30 years, mature and grow up. It has been very rewarding to observe their gratitude and their joy as their LDL-C levels have been lowered further and further with these novel therapies.

Over the forthcoming years I plan to build on my research, individually and together with my national and international collaborators, to develop novel and exciting projects that have emanated from my current research work.

One area of future research is to prioritize the identification of FH in our black African population. Following a generous donation from Evan Stein, a Wits graduate, the *Evan Stein Centre for Familial Hypercholesterolaemia* was established at the University of the Witwatersrand in 2015 to assist with the identification and treatment of people with FH in South Africa. To date over 1000 FH patients and their family members have been screened. The project will continue until at least 2023 and a priority is to identify more black African subjects with FH as we know very little about the prevalence of FH in this population group. With a population of over 40 million, there should be approximately 130 000 black Africans with FH in South Africa alone, but very few have been identified and very few are receiving lipid lowering medication. This is therefore a very important area of future research. I have two postgraduates involved in research in this area. Natalie Smyth is investigating next generation sequencing of black African subjects with both low and high LDL-C levels in order to try to identify both LDL-C lowering and LDL-C raising variants in this population group. Dr Reinhardt Hesse will be using machine learning on biochemical data, based on laboratory lipid profiles, for the prediction of mutation presence in suspected FH cases. Another area of interest is Lp(a), an independent risk factor for atherosclerotic cardiovascular disease. Whether Lp(a) contributes to atherosclerotic cardiovascular disease in the black African population remains unknown.

My international collaboration and networking will continue and will hopefully expand so that I can continue to contribute to international clinical research in the field of lipidology and atherosclerosis, particularly in the field of familial hypercholesterolaemia, the most common inherited disease in man.