EPIDEMIOLOGY, PATHOGENESIS AND MANAGEMENT OF ATRIAL FIBRILLATION

A thesis submitted for the degree of Doctor of Philosophy

December 2014

Dr Christopher Xin Jie Wong MBBS

Centre for Heart Rhythm Disorders
South Australian Health and Medical Research Institute
University of Adelaide and Royal Adelaide Hospital
“If I have seen further, it is by standing on the shoulders of giants.”

Sir Isaac Newton
DEDICATION

To my parents, Charles and Siew Jee, and my wife Michelle.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEDICATION</td>
<td>2</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>3</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>10</td>
</tr>
<tr>
<td>DECLARATION</td>
<td>12</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>13</td>
</tr>
<tr>
<td>PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES</td>
<td>14</td>
</tr>
<tr>
<td>PRIZES AND AWARDS</td>
<td>21</td>
</tr>
<tr>
<td>CHAPTER 1: LITERATURE REVIEW</td>
<td>22</td>
</tr>
<tr>
<td>1.1 Epidemiology of atrial fibrillation</td>
<td>22</td>
</tr>
<tr>
<td>1.1.1 Incidence of atrial fibrillation</td>
<td>22</td>
</tr>
<tr>
<td>1.1.2 Prevalence of atrial fibrillation</td>
<td>25</td>
</tr>
<tr>
<td>1.1.3 Traditional risk factors for atrial fibrillation</td>
<td>28</td>
</tr>
<tr>
<td>1.1.4 Emerging risk factors for atrial fibrillation</td>
<td>31</td>
</tr>
<tr>
<td>1.1.5 Racial differences in atrial fibrillation</td>
<td>33</td>
</tr>
<tr>
<td>1.1.6 Genetic differences in atrial fibrillation</td>
<td>35</td>
</tr>
<tr>
<td>1.2 Morbidity and mortality associated with atrial fibrillation</td>
<td>37</td>
</tr>
<tr>
<td>1.2.1 Thromboembolism associated with atrial fibrillation</td>
<td>37</td>
</tr>
<tr>
<td>1.2.2 Congestive cardiac failure associated with atrial fibrillation</td>
<td>40</td>
</tr>
<tr>
<td>1.2.3 Sinus node disease and syncope associated with atrial fibrillation</td>
<td>40</td>
</tr>
<tr>
<td>1.2.4 Other cardiovascular diseases associated with atrial fibrillation</td>
<td>41</td>
</tr>
<tr>
<td>1.2.5 Cognitive impairment associated with atrial fibrillation</td>
<td>41</td>
</tr>
</tbody>
</table>
1.2.6 Mortality associated with atrial fibrillation .......................... 42
1.3 Management strategies for atrial fibrillation .......................... 43
  1.3.1 Acute management of atrial fibrillation .......................... 43
  1.3.2 Thromboembolic risk reduction in atrial fibrillation ............ 44
    1.3.2.1 Anticoagulation in atrial fibrillation ....................... 44
    1.3.2.2 Novel anticoagulants in atrial fibrillation ................. 47
    1.3.2.3 Antiplatelet therapy in atrial fibrillation ................. 49
    1.3.2.4 Nonpharmacologic strategies .......................... 50
  1.3.3 Rate control for atrial fibrillation .......................... 51
  1.3.4 Rhythm control for atrial fibrillation .......................... 53
  1.3.5 Other therapies for atrial fibrillation .......................... 55
1.4 Public health and economic burden of atrial fibrillation ........... 57
  1.4.1 Hospitalisations for atrial fibrillation ....................... 57
  1.4.2 Emergency department visits for atrial fibrillation ........... 58
  1.4.3 Outpatient services for atrial fibrillation .................... 59
  1.4.4 Economic costs associated with atrial fibrillation .......... 59
1.5 Pathogenesis of atrial fibrillation ..................................... 61
  1.5.1 Electrophysiological basis of atrial fibrillation ............... 61
  1.5.2 Rate-related remodelling of the atria .......................... 63
  1.5.3 Atrial substrates in predisposing conditions .................. 65
1.6 Obesity and atrial fibrillation ........................................... 67
  1.6.1 Population studies in obesity and atrial fibrillation ........ 67
  1.6.2 Mechanistic studies in obesity and atrial fibrillation ....... 68
    1.6.2.1 Structural remodelling in obesity ....................... 68
    1.6.2.2 Electrical abnormalities in obesity ..................... 69
4.4 Discussion........................................................................................................ 122
   4.4.1 Major findings ......................................................................................... 122
   4.4.2 Epidemic of atrial fibrillation ................................................................. 122
   4.4.3 Obesity and atrial fibrillation ................................................................. 123
   4.4.4 Limitations ............................................................................................. 124
4.5 Conclusion ..................................................................................................... 125

CHAPTER 5: PERICARDIAL FAT AND ATRIAL FIBRILLATION .................. 146
5.1 Introduction .................................................................................................. 146
5.2 Methods ....................................................................................................... 147
   5.2.1 Study population .................................................................................... 147
   5.2.2 Cardiac magnetic resonance imaging protocol and analysis .................. 148
   5.2.3 Risk factor definitions ........................................................................... 149
   5.2.4 Electrophysiology study and ablation ................................................... 149
   5.2.5 Follow-up .............................................................................................. 150
   5.2.6 Statistical analysis ................................................................................. 150
5.3 Results .......................................................................................................... 153
   5.3.1 Patient characteristics .......................................................................... 153
   5.3.2 Pericardial fat and atrial fibrillation presence ....................................... 153
   5.3.3 Pericardial fat and atrial fibrillation severity ....................................... 153
   5.3.4 Pericardial fat and atrial fibrillation recurrence ................................... 154
   5.3.5 Pericardial fat and left atrial volume .................................................... 155
5.4 Discussion .................................................................................................... 156
   5.4.1 Major findings ....................................................................................... 156
   5.4.2 Pericardial fat and atrial fibrillation ...................................................... 156
5.4.3 Pericardial fat and cardiac structure .................................. 157
5.4.4 Potential mechanisms ....................................................... 158
5.4.5 Implications ................................................................. 159
5.4.6 Limitations ................................................................. 160

5.5 Conclusion ............................................................................ 161

CHAPTER 6: ATRIAL FIBRILLATION IN INDIGENOUS AND NON-
INDIGENOUS AUSTRALIANS .................................................... 170

6.1 Introduction ......................................................................... 170
6.2 Methods .............................................................................. 171
  6.2.1 Data source .................................................................... 171
  6.2.2 Data collection ............................................................. 171
  6.2.3 Echocardiographic study ............................................... 172
  6.2.4 Statistical analysis ....................................................... 172
6.3 Results ................................................................................ 173
  6.3.1 Patient characteristics .................................................. 173
  6.3.2 Race and atrial fibrillation ............................................. 173
  6.3.3 Predictors of atrial fibrillation ........................................ 174
  6.3.4 Echocardiographic measurements ............................... 174
  6.3.5 Hospital utilisation ...................................................... 175
6.4 Discussion ............................................................................ 176
  6.4.1 Major findings ............................................................. 176
  6.4.2 Evidence for racial variation in atrial fibrillation ............. 176
  6.4.3 Possible reasons underlying racial differences in atrial
        fibrillation ................................................................. 177
  6.4.4 Implications ................................................................. 179
  6.4.5 Limitations ................................................................. 180
ABSTRACT

Atrial fibrillation is the most common heart rhythm disorder. Once considered to be a benign condition, it is now known to be associated with significant morbidity and mortality. The rising incidence and prevalence of atrial fibrillation has thus led to growing concern by clinicians and policymakers. In recent years, there have been marked strides in our mechanistic understanding of atrial fibrillation that, coupled with technological advances, have allowed for many new therapies. Despite the resultant explosion in research on atrial fibrillation, however, innumerable uncertainties regarding this intriguing arrhythmia still remain. This has provided fertile ground for the work undertaken as part of this thesis and future research on this condition.

Previous studies contributing to our current understanding of atrial fibrillation are first reviewed in Chapter 1. Chapter 2 subsequently characterises the population burden of atrial fibrillation on the Australian healthcare system by analysing nationwide trends in hospitalisations. To provide some insight into the determinants of such healthcare utilisation, and how they may potentially be modified, Chapter 3 analyses relevant patient- and management-specific factors as they pertain to these trends. Data on two other cardiovascular conditions, myocardial infarction and heart failure, are contrasted with those for atrial fibrillation to provide context and insight into these trends.

Given the emerging epidemic of obesity, Chapter 4 characterises the contribution of obesity to the risk of atrial fibrillation in various clinical situations by undertaking
comprehensive systematic reviews and meta-analyses. In Chapter 5, the possible contribution of pericardial fat in mediating the relationship between obesity and atrial fibrillation is further studied.

In Chapter 6, race-specific differences in atrial fibrillation are explored by analysing differences in the prevalence of atrial fibrillation between Indigenous and non-Indigenous Australians. An insight into possible mechanisms underlying these differences are subsequently provided by studying cardiac structural characteristics. Given the greater prevalence of atrial fibrillation and burden of stroke experienced by Indigenous Australians, in Chapter 7 the race-specific management of atrial fibrillation is characterised with regards to anticoagulation practices.

Finally, insights into the epidemiology, pathogenesis and management of atrial fibrillation from the research presented in this thesis are placed in the context of the previous literature in Chapter 8, before possible directions for future studies on atrial fibrillation are discussed in Chapter 9.
DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree of diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Dr Christopher Xin Jie Wong
December 2014
ACKNOWLEDGEMENTS

This doctoral thesis, and the results within it, would not have been possible without the help and assistance of many. Indeed, I am indebted to numerous people throughout my incredible journey into the world of medical research.

Almost ten years ago, I was privileged to first meet Professor Prashanthan Sanders. Despite my youth and inexperience, Professor Sanders generously took me under his wing and introduced me to research. This fortuitous beginning was to subsequently lead to my fascination with cardiology, and ultimately, the undertaking of this doctorate. Professor Sanders has been an inspiring figure to learn from and I am truly grateful for his unwavering mentorship and support. While a number of years have elapsed already, I hope this represents only the beginning of a long and fruitful collaboration. I am additionally very thankful to A/Professor Kurt Roberts-Thomson, my co-supervisor, who has also been an immense source of direction and invaluable advice over the last few years. In addition to his academic talents and leadership, I admire his ability to successfully and good-naturedly balance clinical work, research, family and more. Similarly, I look forward to continuing to work and collaborate with him in the years ahead.

There have been a number of other researchers that I have learnt much from working with and whose friendship I am grateful for. I worked closely with Dr Martin Stiles when I first started, who was incredibly patient in teaching me the basics of electrophysiology and research. Dr Dennis Lau has always been incredibly generous with his time, offering insightful advice on research and life. Dr Scott Willoughby was an early supervisor and I am very grateful for his guidance. Dr Anthony Brooks provided much initial statistical and research education and whose humour always made the office environment enjoyable. Many other electrophysiology fellows, doctoral students themselves or other researchers have also taught me much and made the group a pleasure to work with over the years, including Drs Bobby John, Hany Dimitri, Han Lim, Muayad Alasady, Darryl Leong, Gautam Sharma, Narayan Namboodiri, Anand Ganesan, Rajiv Mahajan, Rajeev Pathak, Sachin Nayyar, Darragh Twomey, Pawel Kuklik and Nicholas Shipp. Thomas Sullivan also taught me much about statistics, Lauren Wilson assisted me greatly in electrophysiology matters, and Melissa Middeldorp helped me significantly on many areas over the years. I have also learned much from close collaborations with other consultants and leading clinical academics, including Professors Stephen Worthley and Joseph Selvanayagam, and A/Professors Matthew Worthley and Glenn Young. Too many to mention are my many other colleagues and friends, whom I am thankful to for all their support and encouragement over the years.

Finally, I would like to make a special thanks to my family – my parents Dr Charles Wong and Mrs Siew Jee Wong, and my sisters Drs Michelle and Nicole Wong – whose love, support and guidance have enabled every opportunity I have had in life. Most importantly, I thank my wife, Dr Michelle Sun, without whose love, support, encouragement, patience and more, none of this would be possible.
PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

Chapter One

1. **Editorial**: Wong CX, Lau DH, Sanders P. Atrial Fibrillation Epidemic and Hospitalizations: How to Turn the Rising Tide? *Circulation 2014*; 129(23):2361-3


Chapter Two

1. **Manuscript**: Wong CX, Brooks AG, Leong DP, Roberts-Thomson KC, Sanders P. The Increasing Burden of Atrial Fibrillation Compared to Heart Failure and Myocardial Infarction: A 15 Year Study of All Hospitalizations in Australia. *Archives of Internal Medicine 2012*; 172(9):739-741


4. **Presentation:** Wong CX, Sun MT, Lau DH, Brooks AG, Leong DP, Shipp NJ, Alasady M, Lim HS, Abed HS, Sanders P. Increases in Atrial Fibrillation Hospitalization Rates are Greater than Myocardial Infarction or Heart Failure: A 15-Year Nationwide Study. *Heart Rhythm 2011*

**Chapter Three**


Chapter Four


**Chapter Five**


Chapter Six


Chapter Seven

PRIZES AND AWARDS

1. Royal Adelaide Hospital Nimmo Professorial Prize, 2011
2. National Health and Medical Research Council of Australia Postgraduate Scholarship, 2012
3. Cardiac Society of Australia and New Zealand McCredie/Wilcken Fellowship, 2012
4. National Heart Foundation of Australia Travel Grant, 2012
5. SA Heart Research Award, 2012
6. Royal Adelaide Hospital David Taverner Scholarship, 2012
7. Florey Medical Research Foundation Postgraduate Scholarship, 2013
8. University of Adelaide Discipline of Medicine Travel Grant, 2013