

**EPIDEMIOLOGY, PATHOGENESIS AND MANAGEMENT OF
ATRIAL FIBRILLATION**

A thesis submitted for the degree of Doctor of Philosophy

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“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.

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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 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 or 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.

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Dr Christopher Xin Jie Wong

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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
2. Manuscript: Wong CX, Mahajan R, Pathak R, Sanders P. Pericardial and Epicardial Fat: Role in Atrial Fibrillation Pathophysiology and Ablation Outcomes. ***Journal of Atrial Fibrillation* 2013;** *5(5):37-43*

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*
2. Letter: Wong CX, Roberts-Thomson KC, Sanders P. The Burden of Hospitalizations for Atrial Fibrillation. ***Archives of Internal Medicine* 2012;**
172(22):1770
3. Editorial: Wong CX, Lau DH, Sanders P. Atrial Fibrillation Epidemic and Hospitalizations: How to Turn the Rising Tide? ***Circulation* 2014;**
129(23):2361-3

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

1. Manuscript: Wong CX, Brooks AG, Lau DH, Leong DP, Sun MT, Sullivan T, Roberts-Thomson KC, Sanders P. Factors Associated With the Epidemic of Hospitalizations Due to Atrial Fibrillation. ***American Journal of Cardiology 2012***; 110(10):1496-9
2. Manuscript: Wong CX, Sun MT, Lau DH, Leong DP, Brooks AG, Sullivan T, Worthley MI, Roberts-Thomson KC, Sanders P. Nationwide Trends in the Incidence of Acute Myocardial Infarction in Australia, 1993-2010. ***American Journal of Cardiology 2013***; 112(2):169-73
3. Presentation: Wong CX, Brooks AG, Sun MT, Lau DH, Leong DP, Pathak R, Mahajan R, Worthley MI, Roberts-Thomson KC, Sanders P. Global Variation in the Incidence of Myocardial Infarction: Increasing Nationwide Trends in Australia from 1993 to 2010. ***Circulation 2012***

Chapter Four

1. Manuscript: Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp, Twomey D, Ganesan AN, Rangnekar G, Roberts-Thomson KC, Lau DH, Sanders P. Obesity and the Risk of Incident, Post-operative and Post-ablation Atrial Fibrillation: A Meta-Analysis of 626,603 Individuals in 51 Studies. ***JACC Clinical Electrophysiology (in press)***
2. Presentation: Wong CX, Sun MT, Mahajan R, Pathak R, Leong DP, Lau DH, Roberts-Thomson KC, Sanders P. Obesity and the Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis. ***Circulation 2012***
3. Presentation: Wong CX, Sun MT, Pathak R, Mahajan R, Lau DH, Roberts-Thomson KC, Sanders P. Body Mass Index Predicts Postoperative Atrial Fibrillation: Results of a Contemporary Meta-Analysis. ***Circulation 2012***
4. Presentation: Wong CX, Brooks AG, Sun MT, Sullivan T, Lau DH, Leong DP, Ganesan AN, Roberts-Thomson KC, Sanders P. Obesity and Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis. ***Heart, Lung and Circulation 2012***
5. Presentation: Wong CX, Brooks AG, Sun MT, Lau DH, Sullivan T, Leong DP, Roberts-Thomson KC, Sanders P. Body Mass Index Predicts Postoperative Atrial Fibrillation: Results of a Contemporary Meta-Analysis. ***Heart, Lung and Circulation 2012***

6. Presentation: Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, Twomey D, Ganesan AN, Rangnekar G, Roberts-Thomson KC, Lau DH, Sanders P. Obesity and Post-Ablation Atrial Fibrillation. ***Heart Rhythm 2015***
7. Presentation: Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, Twomey D, Ganesan AN, Rangnekar G, Roberts-Thomson KC, Lau DH, Sanders P. Body Mass Index and Recurrent Atrial Fibrillation Following Catheter Ablation. ***European Heart Journal 2015***

Chapter Five

1. Manuscript: Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, Leong DP, Lau DH, Middeldorp ME, Roberts-Thomson KC, Wittert GA, Abhayaratna W, Worthley SG, Sanders P. Pericardial Fat is Associated with Atrial Fibrillation Severity and Ablation Outcome. ***Journal of the American College of Cardiology 2011; 57(17):1745-1751***
2. Manuscript: Wong CX, Mahajan R, Pathak R, Sanders P. Pericardial and Epicardial Fat: Role in Atrial Fibrillation Pathophysiology and Ablation Outcomes. ***Journal of Atrial Fibrillation 2013; 5(5):37-43***
3. Letter: Wong CX, Abed HS, Molaee P, Sanders P. Distinction of 'Fat Around the Heart'. ***Journal of the American College of Cardiology 2011; 58(15)1640-1641***

4. Presentation: Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Leong DP, Lau DH, Roberts-Thomson K, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat is Associated with Left Atrial Structure and Function: Implications for Atrial Fibrillation. ***Circulation 2012***
5. Presentation: Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Leong DP, Lau DH, Roberts-Thomson K, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat is Associated with Left Atrial Structure and Function: Implications for Atrial Fibrillation. ***Heart, Lung and Circulation 2012***
6. Presentation: Wong CX, Abed HS, Molaee P, Mahajan R, Nelson AJ, Roberts-Thomson KC, Wittert GA, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat is Associated with Left Atrial Structure and Function: Implications for Atrial Fibrillation. ***Heart Rhythm 2012***
7. Presentation: Wong CX, Sun MT, Mahajan R, Pathak R, Brooks AG, Lau DH, Roberts-Thomson KC, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat Predicts Reverse Remodeling of the Left Atrium Following Atrial Fibrillation Ablation. ***European Heart Journal 2013***
8. Presentation: Wong CX, Sun MT, Mahajan R, Pathak R, Brooks AG, Lau DH, Roberts-Thomson KC, Abhayaratna WP, Worthley SG, Selvanayagam JB, Sanders P. Pericardial Fat Reduction and Reverse Remodeling Following Atrial Fibrillation Ablation. ***Heart, Lung and Circulation 2013***

Chapter Six

1. Manuscript: Wong CX, Brooks AG, Cheng Y, Lau DH, Rangnekar G, Roberts-Thomson KC, Kalman JM, Brown A, Sanders P. Atrial Fibrillation in Indigenous and Non-Indigenous Australians: A Cross-Sectional Study. **BMJ Open 2014; 4(10):6242**
2. Presentation: Wong CX, Cheng Y, Sun MT, Lau DH, Brooks AG, Shipp NJ, Alasady M, Lim HS, Abed HS, Sanders P. Atrial Fibrillation in Indigenous Australians: Race-Specific Differences. **Heart Rhythm 2011**

Chapter Seven

1. Manuscript: Wong CX, Lee SW, Gan S, Mahajan R, Rangnekar G, Pathak RK, Twomey D, Schultz C, Ganesan AN, Brooks AG, Roberts-Thomson KC, Brown A, Lau DH, Sanders P. Underuse and Overuse of Anticoagulation for Atrial Fibrillation: A Study in Indigenous and Non-Indigenous Australians. **International Journal of Cardiology (in press)**
2. Presentation: Wong CX, Lee SW, Gan S, Mahajan R, Rangnekar G, Pathak RK, Twomey D, Schultz C, Ganesan AN, Brooks AG, Roberts-Thomson KC, Brown A, Lau DH, Sanders P. Guideline Adherence to Anticoagulation for Atrial Fibrillation: A Study in Indigenous and Non-Indigenous Australians. **European Heart Journal 2015**

3. Presentation: Wong CX, Lee SW, Gan S, Mahajan R, Rangnekar G, Pathak RK, Twomey D, Schultz C, Ganesan AN, Brooks AG, Roberts-Thomson KC, Brown A, Lau DH, Sanders P. Underuse and Overuse of Anticoagulation for Atrial Fibrillation: A Study in Indigenous and Non-Indigenous Australians. ***Heart Rhythm 2015***

PRIZES AND AWARDS

1. Royal Adelaide Hospital Nimmo Professorial Prize, 2011
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