2018 Barbara Mawer Travelling Fellowship Final Report Alexander J. Rodriguez

Project: “Is bisphosphonate use associated with heart failure?”

First of all, I wish to again express my profound gratitude to the Society for welcoming my membership and for this extraordinary opportunity. Outside of the specific aims of the project undertaken, this Fellowship has resulted in two important personal outcomes: (1) I fulfilled the initial motivation for my study in learning sophisticated epidemiological techniques and (2) I have cultivated valuable professional contacts and enhanced my research profile which will both contribute to future research success as I transition from student to professional.

My project aimed to understand if use of the common anti-osteoporosis agent bisphosphonates was associated with increased risk of heart failure. Our present understanding is that fractures are associated with an increased mortality risk and that having low bone mineral density (BMD) is also associated with an increased risk of mortality. The causal nature of the relationship between fractures, low BMD and mortality remains controversial. Most individuals, particularly in developed countries, die as a result of cardiovascular diseases (CVD). Presently, it is uncertain if the excess mortality related to low BMD and fractures is due to a potential indirect mechanism that arises from the treatment of osteoporosis. Bisphosphonates, a widely used anti-osteoporosis drug, have been previously linked to an increase in cardiovascular risk but causality remains controversial. Previous studies were limited in their investigation of prognostic factors for heart failure as the data capture was from insurance records and not clinical records. Therefore, taking into consideration important risk factors such as hypertension, renal function, body composition, smoking and other risk behaviours; it is anticipated that we may be able to potentially better characterise the risk of heart failure from bisphosphonate therapy and further, better identify specific patient sub-sets who may be at elevated risk levels.

I undertook this project at the University of Southern Denmark in Odense, Denmark. Here I worked with the Odense Patient data Exploratory Network (OPEN) under the guidance of Professor Bo Abrahamsen. The OPEN team consists of clinicians, statisticians, epidemiologists and academic scientists. This setting was ideal from a mentorship and also study design perspective. The cohort that I examined all had hip and spine BMD assessed by dual-energy x-ray absorptiometry (DXA) meaning that compared to previous investigations, patients and controls in this study were matched by indication. Other similar studies were confounded by control patients (those not receiving treatment) not having BMD information limiting the ability to independently examine the contribution of BMD to risks. Also, a unique aspect of the Danish health system is the centralised archiving of information through Statistics Denmark. All registries for the various confounders and outcomes we were interested in were complete in the sense that there were no missing data – phew!

There were approximately 7,500 patients who had a prescription for bisphosphonates and we matched these patients using a technique called propensity score matching, to approximately 20,000 controls who never used bisphosphonates. A propensity score is the conditional probability that an individual receives a treatment or exposure under study (in this case, a bisphosphonate prescription) given all measured confounders. Thus, by propensity score matching we are able to, as best

we can, replicate the randomisation performed in clinical trials and limit bias by robustly accounting for differences between users and non-users. This was an unanticipated technique I picked up as part of my project.

The rate of atrial fibrillation and heart failure events amongst bisphosphonate users was approximately 60% that of non-users when assessing crude incidence rates. However, in Cox-proportional models bisphosphonate use was associated with an approximate 20% increased risk of atrial fibrillation and 10% increased risk of heart failure in a minimally adjusted analysis. After adjusting for multiple potential confounders these associations were attenuated: approximate 10% increased risk of atrial fibrillation and approximate 5% decreased risk of heart failure (non-significant). Employing the defined daily dosage (DDD) strategy to estimate cumulative drug exposure did not appear to change these findings.

These findings were surprising as during my study tour a very similar study to the one I was undertaking was published and showed that bisphosphonate use was robustly associated with decreased risk of many cardiovascular events (including atrial fibrillation and heart failure) as well as atherosclerotic events and mortality [doi: https://doi.org/10.1002/jbmr.3448]. We were fortunate that in our study all patients had BMD by DXA and thus we were able to investigate the independent contribution of low bone mass to event risks. Thus, we additionally adjusted our models for BMD and separately for T-score, but results remained unchanged. This led us to speculate that any risks associated with long-term bisphosphonate use on cardiac dynamics may be due to mechanisms independent of bone mass and may be more related to direct effects of bisphosphonates on cardiac tissue. Investigation of this hypothesis is informing my future work.

As with many aspects of life it is the , what I like to call “Donald Rumsfelds” (“unknown-unknowns”) that always seem to have the greatest positive impact you. It was learning the propensity score matching technique that has massively added to my epidemiological skillset and something that will be immediately applicable to my ongoing work. Another Rumsfeld I picked up was in how the data for the cohort is organised and managed. In my previous work I would usually compile all the data I need into the one dataset and get analysing. However, in wanting to keep to the OPEN model, the approach was instead to keep related information in separate datasets (eg. all prescription information in one, all DXA information in another etc.) and then at the time of analysis use some commands to “reach” into these datasets to use only the information I needed and created a temporary dataset that exists only at the time of analysis. This made data management more streamlined, file sizes were smaller and also there was less chance of carrying forward any errors. I will certainly be employing this data management strategy in my future work.

Overall, this experience has been enormously rewarding. I have gained many new professional skills that I can immediately employ in my current research as I finish my PhD and also take into future research for which this study tour has sparked many interesting hypotheses. I have also made many new contacts, some that have been professional mentors and others that may prove to be potential collaborators for future work. I wish to thank, most sincerely the BRS for this incredible opportunity. I hope that my experience outlined here provides the Society with satisfaction that, yet another young researcher has benefitted from the generous and unique support offered through the Fellowship.