Elsevier Editorial System(tm) for Heart, Lung and Circulation

Manuscript Draft

Manuscript Number: HLC-D-17-00158R1

Title: Increased admissions due to cardiac complications of thyrotoxicosis in Māori

Article Type: Original Article

Section/Category: Indigenous Cardiovascular Health

Keywords: hyperthyroidism; Graves' disease; congestive heart failure; atrial fibrillation; toxic multinodular goitre

Corresponding Author: Dr. Marianne S Elston, MB ChB, PhD

Corresponding Author's Institution: Waikato Hospital

First Author: Jade A Tamatea

Order of Authors: Jade A Tamatea; Marianne S Elston, MB ChB, PhD; John V Conaglen

Abstract:
Background
As thyrotoxicosis is a risk factor for atrial fibrillation current guidelines recommend measuring a thyroid-stimulating hormone level in patients with this disorder. Hyperthyroidism may also be associated with other heart disease including cardiac ischaemia and cardiac failure. Currently the prevalence of thyrotoxicosis in cardiac admissions in the absence of a rhythm disorder is unknown.
Aims: The aims of this study were: 1) to calculate the prevalence of admissions for thyrotoxicosis-associated cardiac disease, 2) determine the type of cardiac disease i.e. dysrhythmic, ischaemic or cardiac failure, and 3) to assess whether Māori are over-represented amongst patients admitted to hospital with cardiac complications of thyrotoxicosis.
Methods
A retrospective review of admissions with both thyrotoxicosis and cardiac disease from January 1st 2005 to December 31st 2012 inclusive.
Results
Seventy-two patients were identified as being admitted for a cardiac complication of thyrotoxicosis, giving a mean of 9 admissions per year. Dysrhythmia was the cause for admission in 32 patients, ischaemia in 12, cardiac failure in 11 and mixed cardiac disease in 17. Graves' disease and amiodarone-induced were the most common causes of the thyrotoxicosis (25 and 19 cases, respectively). Of the cohort 26 (36.1%) were Māori (compared to 16.8% of all cardiac admissions over the same period). Māori were more likely to present with cardiac failure than non-Māori (57.7% vs. 26.1%, p=0.008 respectively).
Conclusions
Māori are over-represented amongst patients admitted with cardiac complications of thyrotoxicosis and more often present with cardiac failure than non-Māori. Measurement of thyroid function should be considered in patients presenting not only with atrial fibrillation but

also in patients presenting with cardiac failure, particularly if they are Māori.

3 September 2017

Lavanya Ashwin
Journal Manager
Heart, Lung, and Circulation

Dear Lavanya,

Re: HLC-D-17-00158 “Increased admissions for cardiac complications of thyrotoxicosis in Māori”.

Thank you for the opportunity to revise this manuscript. We believe that we have addressed all the reviewers’ comments and that the article is now suitable for publication in *Heart, Lung, and Circulation.*

We accept full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. There are no potential conflicts of interest. No external financial support.

Thank you for considering our revision.

Kind regards,

Nāku noa,

Jade AU Tamatea

Title page (including author details)

Increased admissions due to cardiac complications of thyrotoxicosis in Māori

Type of manuscript: Original article, cardiology section

Jade AU Tamatea, Marianne S Elston, John V Conaglen

Waikato Clinical Campus, University of Auckland, Hamilton, New Zealand

Acknowledgements: nil

Corresponding author:

Dr Jade Tamatea

Department of Endocrinology

Waikato Hospital, Private Bag 3200, Hamilton 3240, New Zealand

Email: Jade.Tamatea@waikatodhb.health.nz

Phone: +6478398899

Response to Reviewers

Reviewer #1.

Thank you for your comments.

We have added the phrase "population-based" to the Methods (page4).

Denominator for the prevalence measure… In our institution the majority of admissions for a cardiac cause are either admitted under or care is transferred to the cardiology service. In this cohort, 70.8% of the patients were admitted to the cardiology service. In order to be consistent with both denominator and numerator, for prevalence, only cardiac patients were included. As such it is most appropriate to use as the denominator all cardiac discharges.

As this is a geographically defined population… We agree with the reviewer's comments. We have used the census data from the time period studied. This is included in the results (proportion of Māori as per census for the region). While we could assess the rate of thyrotoxicosis-associated cardiac complications per 10,000 population, as there will be people in the community who have cardiac complications of thyrotoxicosis who are not admitted this figure would be misleading and so instead we have used the rate as per cardiac hospitalisations which would seem more appropriate for this particular study. In addition, we know that cardiac conditions, both ischaemic heart disease and congestive heart failure, have higher prevalence in the Māori population, with increased admission rates for the same. In an attempt to control for this we used cardiac admissions as the denominator of prevalence. If the reviewer believes the incidence of thyrotoxic cardiac admissions for the general population would be of benefit to the reader, we would be happy to include it.

*By my calculations….*As discussed in the earlier point, the numerator used for prevalence calculation was limited to those admitted to the cardiology service (i.e. 51 patients of the greater cohort of 72). It is from this that the prevalence of 14 per 10,000 and 25.0 per 10,000 have come. We thank the reviewer for pointing out the difficulty in interpretation of this result. We have added to the description to clarify this important point made by the reviewer (page 6). The full 72 patient cohort was used in the analysis to describe the cohort.

*The prevalence rate ratio…*We strongly agree with the reviewer, unfortunately this is a small cohort, making age, gender and SES –standardization difficult without producing very small cell sizes. A larger, prospective study with more information, would be better placed to answer this issue. To illustrate the important point, made by the reviewer, we have added age-stratified prevalence rates and ratios to the results (page 7).

Were there any thyrotoxicosis admissions for other cardiac causes? Yes, you are correct there were no cases of thyrotoxicosis identified in the other cardiac diagnoses group as detailed in the discussion on page 10. We have added this to the results section as recommended (page 6).

*Mortality…*Thank you for pointing this out. The mortality rate in the group with thyrotoxicosis and cardiac disease was so low it is difficult to comment further on this and so we have removed this from Table 1. The mortality was over the eight years of the study and was death within the hospitalization.

*The discussion could be enhanced…*In terms of mechanistic suggestions for the disparity suggested this is difficult due to the retrospective nature of the study. We agree that it is possible that this may be at least in part due to disparity in rheumatic heart disease amongst Māori. We have added this to the discussion, page 9. We also have evidence of disparity in thyrotoxicosis from a recent prospective study assessing ethnic differences in the incidence of thyrotoxicosis with the incidence of thyrotoxicosis for Māori being double that of non-Māori. This work is currently in preparation for publication, which is why we have not cited this. As part of this prospective study we have also identified that the journey to specialist assessment is longer for Māori than non-Māori and it is possible that the chronicity of this untreated thyrotoxicosis may contribute to a higher rate of cardiac dysfunction. This we have detailed as a personal communication in the discussion page 9. Recent work has demonstrated that thyrotoxicosis is associated with an increased risk of mortality including that of cardiovascular mortality (HR 1.27) (Giesecke P et al Thyroid 2017). As most patients with thyrotoxicosis do not require admission it is difficult to know whether there is an ethnic difference in mortality amongst patients with thyrotoxicosis but we agree that this would be an important area for future study.
Thank you for reminding us to avoid deficit interpretations. We have reviewed our discussion once more and are happy there are no deficit interpretations presented.

Reviewer #2

We agree it is possible that some appropriate acute cardiac admissions were missed due to lack of coding or that thyroid function was not checked. Unfortunately this is one of the limitations of a retrospective study. We have extended the discussion to elaborate on this page 9. As we mentioned in the discussion given the prevalence of thyrotoxicosis in the community it is surprising that none of the almost 15,000 patients in the other cardiac presentations were not identified as having thyrotoxicosis. However, we do believe that the findings from this study suggest that there may be an ethnic disparity and that a prospective study would be appropriate.

*Analysis of the 72 patients…*We thank you for this point. We have added an age-stratified prevalence rate ratio to the results to consider the implications of the younger age structure of the Māori population, as well as the point you raise, of younger age of cardiac admissions for Māori (in particular with heart failure) (page 7). Unfortunately this study is limited by the small number of cases, making age-standardised prevalence rate ratio difficult to calculate without small cell numbers.

*More information regarding population and admission demographics…*We do not have detailed information for the demographics for the whole population as this paper is not about the ethnic differences in cardiac disease as this has already been well described. We have detailed that Māori comprised 16.8% of the entire cohort which is consistent with the Waikato DHB adult population (17.3% Māori during this time period) and have given the breakdown by the main three cardiac diagnoses which, similar to the literature, shows that Māori are over-represented amongst those presenting with heart failure. We do not have further demographic data (i.e. deprivation data) on this population easily available to us.

*Presentation of results in a graphic form…*We have added a graph of the distribution of cardiac admissions between ethnicities, to help with understanding (Figure 1).

Is there ongoing work? We have put together protocols to assess whether how often thyroid function tests are measured in patients presenting with an acute cardiac condition, and whether there are ethnic differences in measurement of thyroid function as well as that for a prospective study assessing thyroid function in all cardiac admissions however we currently do not have funding available to perform these as both studies are extremely resource intensive (particularly the prospective study due to the high throughput and rapid patient turnover). By identifying a need for further work in this area (i.e. publishing this paper in a reputable journal such as Heart, Lung and Circulation) this will help us in our efforts to source external funding to undertake this work. This is an important area to study further especially given the increased cardiovascular mortality associated with thyrotoxicosis.

Abstract

Background

As thyrotoxicosis is a risk factor for atrial fibrillation current guidelines recommend measuring a thyroid-stimulating hormone level in patients with this disorder. Hyperthyroidism may also be associated with other heart disease including cardiac ischaemia and cardiac failure. Currently the prevalence of thyrotoxicosis in cardiac admissions in the absence of a rhythm disorder is unknown.

Aims: The aims of this study were: 1) to calculate the prevalence of admissions for thyrotoxicosis-associated cardiac disease, 2) determine the type of cardiac disease i.e. dysrhythmic, ischaemic or cardiac failure, and 3) to assess whether Māori are over-represented amongst patients admitted to hospital with cardiac complications of thyrotoxicosis.

Methods

A retrospective review of admissions with both thyrotoxicosis and cardiac disease from January 1st 2005 to December 31st 2012 inclusive.

Results

Seventy-two patients were identified as being admitted for a cardiac complication of thyrotoxicosis, giving a mean of 9 admissions per year. Dysrhythmia was the cause for admission in 32 patients, ischaemia in 12, cardiac failure in 11 and mixed cardiac disease in 17. Graves' disease and amiodarone-induced were the most common causes of the thyrotoxicosis (25 and 19 cases, respectively). Of the cohort 26 (36.1%) were Māori (compared to 16.8% of all cardiac admissions over the same period). Māori were more likely to present with cardiac failure than non-Māori (57.7% vs. 26.1%, p=0.008 respectively).

Conclusions

Māori are over-represented amongst patients admitted with cardiac complications of thyrotoxicosis and more often present with cardiac failure than non-Māori. Measurement of thyroid function should be considered in patients presenting not only with atrial fibrillation but also in patients presenting with cardiac failure, particularly if they are Māori.

Keywords: hyperthyroidism; Graves' disease; congestive heart failure; atrial fibrillation; toxic multinodular goitre

Introduction

Thyrotoxicosis is a common endocrine disorder, which when untreated results in significant morbidity and premature mortality [1]. Cardiovascular disease is a common cause of admission to hospital and is associated with a significant health burden in the community. Hyperthyroidism is a known risk factor for cardiac failure and cardiac dysrhythmias, particularly atrial fibrillation [2-4].

A retrospective study assessing rates of thyroid dysfunction in 250 patients presenting to a New Zealand district hospital with atrial fibrillation reported that 5.2% of these patients had either overt or subclinical hyperthyroidism [5]. The ethnic distribution of patients presenting with atrial fibrillation was reported to be consistent with that expected for the population, although no ethnicity data was provided for those identified to have thyroid dysfunction.

An Australian group reported that Māori presenting with cardiac complications of thyrotoxicosis comprised one-third of the cases presenting to their unit despite only representing 0.007% of their regional population [6]. It was suggested by these authors that Māori women might be at increased risk of cardiac complications of thyrotoxicosis. Māori have previously been reported to have an increased rate of admission and mortality from cardiac failure when compared with the non-Māori population [7]. However, there is no data available on rates of thyrotoxicosis in Māori presenting with cardiac failure.

Current guidelines recommend that patients presenting with atrial fibrillation should have thyroid function measured [8]. Whether thyroid testing should also be routinely performed in patients presenting with ischaemic heart disease and heart failure is less clear.

The aims of this study were: 1) to calculate the prevalence of admission for documented thyrotoxicosis-associated cardiac disease, 2) determine the type of cardiac disease i.e. dysrhythmia, ischaemia or cardiac failure, and 3) to assess whether Māori are over-burdened

with cardiac complications of thyrotoxicosis.

Methods

In this retrospective, population-based cohort study, hospital coding using ICD10 codes was used to identify all hospital admissions to Waikato Hospital, a 600-bed tertiary New Zealand Hospital, in which both cardiac disease and thyrotoxicosis were treated during the same admission over the period January 1st 2005 to December 31st 2012, inclusive. Data was obtained from hospital notes, electronic health records, laboratory, and radiology records.

Two searches were carried out. The first included all patients admitted and coded with thyrotoxicosis as the primary diagnosis during that period, identifying 561 admissions. For this search the following codes were used:

E011 - Iodine-deficiency-related multinodular (endemic) goiter,

E050 - Thyrotoxicosis with diffuse goitre

E051 - Thyrotoxicosis with toxic single thyroid nodule

E052 - Thyrotoxicosis with toxic multinodular goitre

E054 - Thyrotoxicosis factitia

E055 - Thyroid crisis or storm

E058 - Other thyrotoxicosis

E059 - Thyrotoxicosis, unspecified

E079 - Disorder of thyroid, unspecified

Of the 561 admissions, 215 patients were identified as having been admitted to cardiology, general medicine or endocrinology services with most of the remainder being admitted for thyroidectomy and so excluded. Following electronic review of the patient's clinical records, 71 patients were confirmed as having acute cardiac involvement contributing to their admission. A second search was undertaken of all the cardiac admissions during the same time period, where thyrotoxicosis (using the same codes as above) was coded as a secondary

diagnosis or complication. Following review of the electronic notes to determine patients who were thyrotoxic at the time of admission, 36 patients were identified. Patients who developed thyrotoxicosis secondary to treatment of their cardiac condition during that admission were excluded. This second search yielded only 1 additional patient who had not been identified by the first search and resulted in a total of 72 patients for analysis.

The electronic notes of all 72 patients were reviewed in detail and data extracted including: age, gender, ethnicity, cause of thyrotoxicosis (based on clinical, laboratory and imaging results and classified as Graves' disease, toxic multinodular goitre, amiodarone-induced, thyroiditis, and levothyroxine overuse), highest free thyroid hormone values, acute cardiac diagnosis resulting in the current hospitalisation (classified as cardiac failure, ischaemia/infarction, dysrhythmia or mixed). Prevalence of thyrotoxicosis within cardiac admissions was calculated using cardiac discharge data for the same period as the denominator and those patients in the cohort who were discharged by a cardiology team as the numerator. In all cases, ethnicity was taken from hospital records, with a prioritization approach used to classify a single ethnicity to individuals. Ethnicity was then classified into Māori and non-Māori groupings.

This study was registered with the institutional review committee and was conducted in accordance with the New Zealand National Health Advisory Committee's Ethical Guidelines for Observational Studies, and with permission of the Endocrine Department.

Statistical analysis was performed using Stata v 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) Mann-Whitney tests were used for continuous variables (as all were non-parametric) and chi-square or Fisher's exact test for categorical variables (depending on cell frequencies). A $p<0.05$ was used to reject the null hypothesis, unless otherwise specified.

Results

Overall there were 35,337 cardiac admissions during the period studied. Māori accounted for 16.8% of the total cardiac admissions during this time period, which parallels the Māori population in the region (2013 census 17.3% of the Waikato DHB adult population were Māori) [9]. The breakdown of discharge (by coded ICD10 principal diagnosis) included: ischaemic heart disease – 12,352 (35.0%), tachyarrhythmias – 4,455 (12.6%), and heart failure and cardiomyopathies – 3,586 (10.1%). These 20,393 were used to investigate the prevalence of thyrotoxicosis within cardiac admissions. When looking by cardiac diagnosis Māori comprised 13.7% of patients presenting with ischaemic heart disease, 27.8% with cardiac failure and 16.8% of those with tachyarrhythmia.

A total of 72 patients were identified as having thyrotoxicosis-associated cardiac disease giving an average of 9 admissions per annum. Details are shown in Table 1. Graves' disease was the cause of the thyrotoxicosis in 25 patients (34.8%), amiodarone-induced thyrotoxicosis in 19 patients (26.4%), toxic multinodular goitre in 18 (25%), excess levothyroxine replacement in 5 (6.9%) and other causes comprised the remaining 5 cases. The majority (51, 70.8%) were admitted to a cardiology service, with the remaining 29.2% being treated by a medical team.

Using the 51 patients admitted to the cardiology service, the prevalence of thyrotoxicosis within all cardiac hospitalisations was 14.4 per 10,000 admissions (95% CI 10.8, 19.0). When limited to hospitalisations for cardiac ischaemic, heart failure and tachyarrhythmia the prevalence of thyrotoxicosis was 25.0 per 10,000 admissions (95% CI 18.6, 32.9). There were no cases of thyrotoxicosis coded in the group of "other" cardiac diagnoses, which comprised 14, 944 discharges.

Patients with concurrent thyrotoxicosis were more likely to present with a tachyarrhythmia - 47 cases (65.3%), compared to heart failure (27 cases [37.5%]) or cardiac ischaemia (16 cases

[22.2%]). Mixed disease was present in 17/72 patients (≥2 diagnoses). All patients with levothyroxine over-replacement presented with a tachyarrhythmia (atrial fibrillation in four and ventricular tachycardia in one patient) and varied in severity of thyrotoxicosis with an FT_4 level up to 49 pmol/L.

Māori comprised 36.1% of those with thyrotoxicosis-associated cardiac admissions. The prevalence of thyrotoxicosis within Māori admitted with cardiac ischaemic, heart failure and tachyarrhythmia was higher than that seen in non- Māori with the same diagnoses, particularly in those under the age of 65 (overall 46.7 per 10,000 admissions vs. 20.6 per 10,000 admissions; aged 65 and under prevalence rate ratio 1.1 [95% CI 0.1, 4.5; p 0.8573]; aged over 65 prevalence rate ratio 2.3 [95%CI 1.0, 4.9; p0.0271]). Māori admitted with thyrotoxicosis-associated cardiac disease were younger than non-Māori (median age 56.5 vs. 65.5 years, p=0.003) and presented with less dysrhythmia and more cardiac failure (53.9% vs. 71.7%, p=0.126 and 57.7% vs. 26.1%, p=0.008 respectively, Figure 1). There was no difference in severity of thyrotoxicosis between Māori and non-Māori (p=0.568) unless patients with AIT were excluded. AIT accounted for 11/16 cases of severe thyrotoxicosis in non-Māori whereas Māori were no more likely to have AIT than expected for the population demographics (3/19 Māori).

Discussion

Admissions for cardiac complications of thyrotoxicosis were relatively infrequent, averaging just less than one admission per month compared to 368 monthly cardiac admissions over the same time period. Amongst admissions for cardiac conditions that were potentially thyrotoxicosis-related (cardiac ischaemia, tachyarrhythmias and heart failure) the prevalence of thyrotoxicosis was 25.0 per 10,000 admissions. Tachyarrhythmias were the most common thyrotoxicosis-associated cardiac admissions but over one-third of hyperthyroid patients admitted had heart failure and almost one-quarter experienced an acute ischaemic cardiac event. In 23.6% of patients more than one of these cardiac complications were present. Approximately one-third of the cases of thyrotoxicosis were iatrogenic with over one-quarter of the cohort having amiodarone-induced thyrotoxicosis. This is a much higher proportion of amiodarone-induced thyrotoxicosis than would normally be expected in a general thyrotoxic cohort and is likely to reflect the underlying cardiac disease in this cohort. Interestingly, while often considered relatively benign, levothyroxine over-replacement comprised almost 7% of the thyrotoxic cohort, particularly affecting older non-Māori and all had tachyarrhythmias (atrial fibrillation or ventricular tachycardia).

From this retrospective study, Māori appear to have a greater burden of disease than non-Māori when admitted with thyrotoxicosis-associated cardiac disease. Māori patients were younger when compared with non-Māori, reflective of the Māori population demographic, although there was no difference in severity of thyrotoxicosis between the two groups. In addition, the type of cardiac involvement differed between the two groups with Māori patients more commonly experiencing cardiac failure than non-Māori. This parallels the known increased rate of admissions for heart failure in Māori as compared to non-Māori [7], which was also seen within this study period.

A significant limitation of this study is that being retrospective, the reasons for the ethnic

disparity could not be identified. Possible contributors to these ethnic differences include the concepts that both the cardiac and/or thyroid disease in Māori is more severe, or that Māori have higher rates of underlying cardiac disease, such as the known higher rate of rheumatic heart disease when they develop thyrotoxicosis, or that both conditions are more prevalent. It was not clear from the notes as to the duration of thyrotoxicosis prior to presentation, treatment duration, and whether the treatment of their thyrotoxicosis was optimal. The duration of untreated disease during initial work up of thyrotoxicosis is longer in Māori than non-Māori (unpublished observations) and barriers to care in other areas have been shown to contribute to more severe presentations and outcomes for Māori [10]. In addition, there are likely social factors contributing to the discrepancy. Māori are overrepresented in lower socioeconomic deciles [11], which reduces access to medical care. It is possible that a delay in receiving treatment, or under-treatment of thyrotoxicosis may result in a higher rate of cardiac dysfunction.

This health disparity seen for Māori can also be adversely affected by other important comorbidities such as obesity, hypertension, rheumatic heart disease, metabolic syndrome and diabetes mellitus, also known to disproportionately affect Māori [12,13]. Prospective work in this area, accurately quantifying the disparity and reviewing the individual, social and healthcare factors that influence it, is needed to identify areas to make improvements.

Current recommendations are to screen for hyperthyroidism in patients with atrial fibrillation. Given the potential role of thyrotoxicosis in heart failure, and the prevalence of thyrotoxicosis, particularly in Māori, noted in this study it might be suggested that these patients should also be assessed for hyperthyroidism. As this study is retrospective and notes based, it only illustrates the hyperthyroidism that was identified and coded, not what existed, as there may have been additional patients with undiagnosed thyrotoxicosis. There is the potential to under-count thyrotoxicosis in this population, particularly in Māori if there was a bias in testing. This could be avoided with a well-designed prospective cohort study.

Interestingly, there were no cases of thyrotoxicosis in any of the other cardiac diagnoses despite this group being almost 15,000 patients and a background prevalence of thyrotoxicosis in our community of 0.2% [14]. This suggests that a significant number of cases of thyrotoxicosis were missed in these cardiac patients. This is important as not only is thyrotoxicosis very treatable, but thyrotoxicosis is also associated with an increased risk of cardiovascular mortality [15]. In addition, development of a euthyroid state should be expected to improve the cardiac status.

Conclusions

Māori are over-represented amongst patients admitted with cardiac complications of thyrotoxicosis and more often present with cardiac failure than non-Māori. Measurement of thyroid function should be considered in patients presenting not only with atrial fibrillation but patients presenting with cardiac failure, particularly if they are Māori. Further work is needed to understand this disparity, determine whether it also occurs in other indigenous populations and identify effective interventions.

Acknowledgements

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Brandt F, Green A, Hegedus L, Brix TH. A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. Eur J Endocrinol. 2011;165:491-7.

2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344:501-9.

3. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. 2012;345:e7895.

4. Yue WS, Chong BH, Zhang XH, Liao SY, Jim MH, Kung AW, et al. Hyperthyroidism-induced left ventricular diastolic dysfunction: implication in hyperthyroidism-related heart failure. Clin Endocrinol (Oxf). 2011;74:636-43.

5. Kim DD, Young S, Cutfield R. A survey of thyroid function test abnormalities in patients presenting with atrial fibrillation and flutter to a New Zealand district hospital. N Z Med J. 2008;121:82-6.

6. Nigam P, Morton A. Are Maori women at increased risk of cardiac complications of Graves disease? N Z Med J. 2012;125:90-2.

7. Riddell T. Heart failure hospitalisations and deaths in New Zealand: patterns by deprivation and ethnicity. N Z Med J. 2004;118:U1254.

8. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European heart journal. 2010;31:2369-429.

9. Statistics New Zealand. Census quickstats about Māori. 2013 [accessed September 8, 2015]. Available from: http://www.stats.govt.nz/Census/2013-census/profile-and-summary-reports/quickstats-about-maori-english.aspx

10. Robson B, Ellison-Loschmann L. Māori and cancer care in Aotearoa/New Zealand - responses to disparities. European journal of cancer care. 2016;25:214-8.

11. Salmond C, Crampton P, King P, Waldegrave C. NZiDep: A New Zealand index of socioeconomic deprivation for individuals. Soc Sci Med. 2006;62:1474-85.

12. Milne RJ, Lennon DR, Stewart JM, vander Hoorn S, Scuffham PA. Incidence of acute rheumatic fever in New Zealand children and youth. J Paediatr Child Health. 2012;48:685-91.

13. Gentles D, Metcalf P, Dyall L, Sundborn G, Schaaf D, Black P, et al. Metabolic syndrome prevalence in a multicultural population in Auckland, New Zealand. N Z Med J. 2007;120:U2399.

14. Gibbons V, Conaglen JV, Lillis S, Naras V, Lawrenson R. Epidemiology of thyroid disease in Hamilton (New Zealand) general practice. Aust N Z J Public Health. 2008;32:421-3.

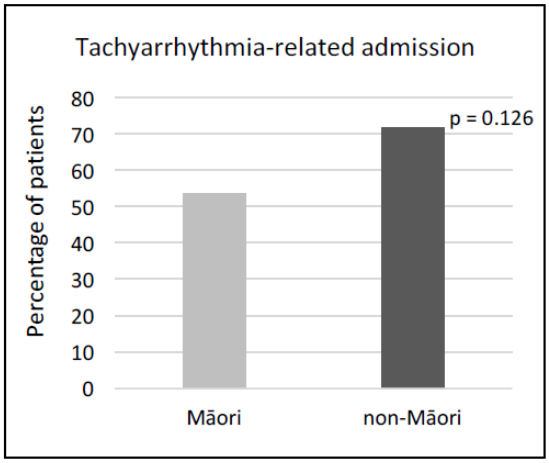
15. Giesecke P, Rosenqvist M, Frykman V, Friberg L, Wallin G, Höijer J, et al. Increased Cardiovascular Mortality and Morbidity in Patients Treated for Toxic Nodular Goiter Compared to Graves' Disease and Nontoxic Goiter. Thyroid. 2017;27:878-885.

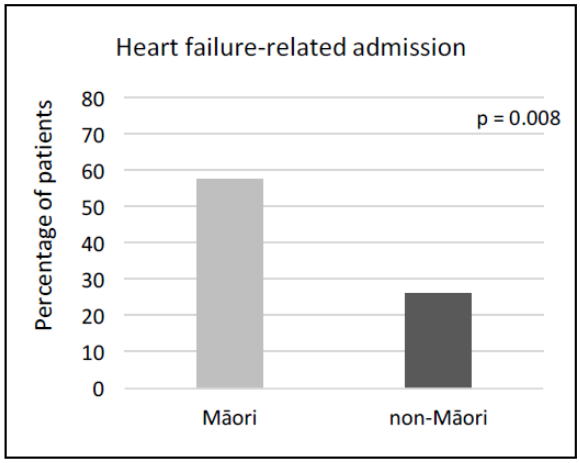
277 **Table 1. Characteristics of patients with thyrotoxicosis-associated cardiac admissions**

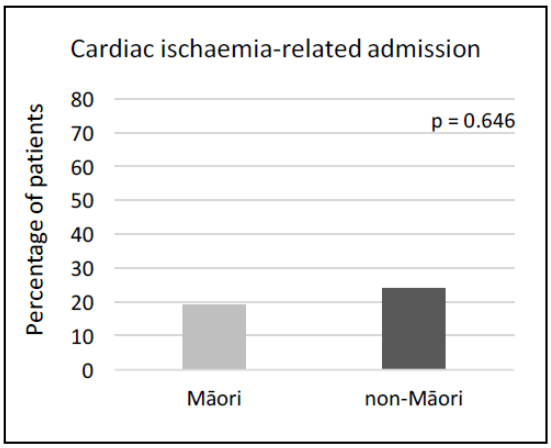
Median age (range)		59.5 (23-88)	
Gender	Female	48 (66.7%)	
Ethnicity	Māori	26 (36.1%)	
	Non-Māori	46 (63.9%)	
Median length of stay (range)		5 days (0-30) - Māori 5 (1-23) - Non- Māori 5 (0-30)	p=0.6334
Thyrotoxicosis cause	Graves' disease	25 (34.8%)	
	AIT	19 (26.4%)	
	TMNG	18 (25%)	
	Thyroxine	5 (6.9%)	
	Other	5 (6.9%)	
Cardiac diagnosis[a]	Tachyarrhythmia	47/72 (65.3%) - Māori 14/26 (53.8%) - Non- Māori 33/46 (71.7%)	p=0.126[b]
	Heart failure	27/72 (37.5%) - Maori 15/26 (57.7%) - Non-Maori 12/46 (26.1%)	p=0.008[b]
	Cardiac ischaemia	16/72 (22.2%) - Maori 5/26 (19.2%) - Non-Maori 11/46 (23.9%)	p=0.646[b]
Severity of thyrotoxicosis FT_4 (RR 12-22 pmol/L)	Mild - FT_4 <30 pmol/L	28/72 (38.9%) - Māori 8/26 - Non- Māori 20/46	
	Moderate - FT4 31-50 pmol/L	17/72 (23.6%) - Māori 7/26 - Non- Māori 10/46	p=0.543
	Severe - FT4 >51 pmol/L	27/72 (37.5%) - Māori 11/26 - Non- Māori 16/46	

AIT = amiodarone-induced thyrotoxicosis; TMNG = toxic multinodular goitre; FT_4 = free thyroxine level; RR = reference range; [a]Patients may have more than one diagnosis so total adds up to more than the total number of patients. [b]Bonferroni adjustment used to recognise multiple diagnoses, $p<0.017$ used to reject the null hypothesis.

282 1.


Tachyarrhythmia-related admission
Percentage of patients
80
70
60
50
40
30
20
10
0
p = 0.126
Māori
non-Māori


Heart failure-related admission
Percentage of patients
80
70
60
50
40
30
20
10
0
p = 0.008
Māori
non-Māori


Cardiac ischaemia-related admission
Percentage of patients
80
70
60
50
40
30
20
10
0
p = 0.646
Māori
non-Māori

283

284

Figure Legends

Figure 1. Percentage of patients presenting with tachyarrhythmia, heart failure or cardiac ischaemia, by ethnicity

Abstract

Background

As thyrotoxicosis is a risk factor for atrial fibrillation current guidelines recommend measuring a thyroid-stimulating hormone level in patients with this disorder. Hyperthyroidism may also be associated with other heart disease including cardiac ischaemia and cardiac failure. Currently the prevalence of thyrotoxicosis in cardiac admissions in the absence of a rhythm disorder is unknown.

Aims: The aims of this study were: 1) to calculate the prevalence of admissions for thyrotoxicosis-associated cardiac disease, 2) determine the type of cardiac disease i.e. dysrhythmic, ischaemic or cardiac failure, and 3) to assess whether Māori are over-represented amongst patients admitted to hospital with cardiac complications of thyrotoxicosis.

Methods

A retrospective review of admissions with both thyrotoxicosis and cardiac disease from January 1st 2005 to December 31st 2012 inclusive.

Results

Seventy-two patients were identified as being admitted for a cardiac complication of thyrotoxicosis, giving a mean of 9 admissions per year. Dysrhythmia was the cause for admission in 32 patients, ischaemia in 12, cardiac failure in 11 and mixed cardiac disease in 17. Graves' disease and amiodarone-induced were the most common causes of the thyrotoxicosis (25 and 19 cases, respectively). Of the cohort 26 (36.1%) were Māori (compared to 16.8% of all cardiac admissions over the same period). Māori were more likely to present with cardiac failure than non-Māori (57.7% vs. 26.1%, p=0.008 respectively).

Conclusions

Māori are over-represented amongst patients admitted with cardiac complications of thyrotoxicosis and more often present with cardiac failure than non-Māori. Measurement of thyroid function should be considered in patients presenting not only with atrial fibrillation but also in patients presenting with cardiac failure, particularly if they are Māori.

Keywords: hyperthyroidism; Graves' disease; congestive heart failure; atrial fibrillation; toxic multinodular goitre

Introduction

Thyrotoxicosis is a common endocrine disorder, which when untreated results in significant morbidity and premature mortality [1]. Cardiovascular disease is a common cause of admission to hospital and is associated with a significant health burden in the community. Hyperthyroidism is a known risk factor for cardiac failure and cardiac dysrhythmias, particularly atrial fibrillation [2-4].

A retrospective study assessing rates of thyroid dysfunction in 250 patients presenting to a New Zealand district hospital with atrial fibrillation reported that 5.2% of these patients had either overt or subclinical hyperthyroidism [5]. The ethnic distribution of patients presenting with atrial fibrillation was reported to be consistent with that expected for the population, although no ethnicity data was provided for those identified to have thyroid dysfunction.

An Australian group reported that Māori presenting with cardiac complications of thyrotoxicosis comprised one-third of the cases presenting to their unit despite only representing 0.007% of their regional population [6]. It was suggested by these authors that Māori women might be at increased risk of cardiac complications of thyrotoxicosis. Māori have previously been reported to have an increased rate of admission and mortality from cardiac failure when compared with the non-Māori population [7]. However, there is no data available on rates of thyrotoxicosis in Māori presenting with cardiac failure.

Current guidelines recommend that patients presenting with atrial fibrillation should have thyroid function measured [8]. Whether thyroid testing should also be routinely performed in patients presenting with ischaemic heart disease and heart failure is less clear.

The aims of this study were: 1) to calculate the prevalence of admission for documented thyrotoxicosis-associated cardiac disease, 2) determine the type of cardiac disease i.e. dysrhythmia, ischaemia or cardiac failure, and 3) to assess whether Māori are over-burdened

with cardiac complications of thyrotoxicosis.

Methods

In this retrospective, population-based cohort study, hospital coding using ICD10 codes was used to identify all hospital admissions to Waikato Hospital, a 600-bed tertiary New Zealand Hospital, in which both cardiac disease and thyrotoxicosis were treated during the same admission over the period January 1st 2005 to December 31st 2012, inclusive. Data was obtained from hospital notes, electronic health records, laboratory, and radiology records.

Two searches were carried out. The first included all patients admitted and coded with thyrotoxicosis as the primary diagnosis during that period, identifying 561 admissions. For this search the following codes were used:

E011 - Iodine-deficiency-related multinodular (endemic) goiter,

E050 - Thyrotoxicosis with diffuse goitre

E051 - Thyrotoxicosis with toxic single thyroid nodule

E052 - Thyrotoxicosis with toxic multinodular goitre

E054 - Thyrotoxicosis factitia

E055 - Thyroid crisis or storm

E058 - Other thyrotoxicosis

E059 - Thyrotoxicosis, unspecified

E079 - Disorder of thyroid, unspecified

Of the 561 admissions, 215 patients were identified as having been admitted to cardiology, general medicine or endocrinology services with most of the remainder being admitted for thyroidectomy and so excluded. Following electronic review of the patient's clinical records, 71 patients were confirmed as having acute cardiac involvement contributing to their admission. A second search was undertaken of all the cardiac admissions during the same time period, where thyrotoxicosis (using the same codes as above) was coded as a secondary

diagnosis or complication. Following review of the electronic notes to determine patients who were thyrotoxic at the time of admission, 36 patients were identified. Patients who developed thyrotoxicosis secondary to treatment of their cardiac condition during that admission were excluded. This second search yielded only 1 additional patient who had not been identified by the first search and resulted in a total of 72 patients for analysis.

The electronic notes of all 72 patients were reviewed in detail and data extracted including: age, gender, ethnicity, cause of thyrotoxicosis (based on clinical, laboratory and imaging results and classified as Graves' disease, toxic multinodular goitre, amiodarone-induced, thyroiditis, and levothyroxine overuse), highest free thyroid hormone values, acute cardiac diagnosis resulting in the current hospitalisation (classified as cardiac failure, ischaemia/infarction, dysrhythmia or mixed). Prevalence of thyrotoxicosis within cardiac admissions was calculated using cardiac discharge data for the same period as the denominator and those patients in the cohort who were discharged by a cardiology team as the numerator. In all cases, ethnicity was taken from hospital records, with a prioritization approach used to classify a single ethnicity to individuals. Ethnicity was then classified into Māori and non-Māori groupings.

This study was registered with the institutional review committee and was conducted in accordance with the New Zealand National Health Advisory Committee's Ethical Guidelines for Observational Studies, and with permission of the Endocrine Department.

Statistical analysis was performed using Stata v 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.) Mann-Whitney tests were used for continuous variables (as all were non-parametric) and chi-square or Fisher's exact test for categorical variables (depending on cell frequencies). A $p<0.05$ was used to reject the null hypothesis, unless otherwise specified.

Results

Overall there were 35,337 cardiac admissions during the period studied. Māori accounted for 16.8% of the total cardiac admissions during this time period, which parallels the Māori population in the region (2013 census 17.3% of the Waikato DHB adult population were Māori) [9]. The breakdown of discharge (by coded ICD10 principal diagnosis) included: ischaemic heart disease – 12,352 (35.0%), tachyarrhythmias – 4,455 (12.6%), and heart failure and cardiomyopathies – 3,586 (10.1%). These 20,393 were used to investigate the prevalence of thyrotoxicosis within cardiac admissions. When looking by cardiac diagnosis Māori comprised 13.7% of patients presenting with ischaemic heart disease, 27.8% with cardiac failure and 16.8% of those with tachyarrhythmia.

A total of 72 patients were identified as having thyrotoxicosis-associated cardiac disease giving an average of 9 admissions per annum. Details are shown in Table 1. Graves' disease was the cause of the thyrotoxicosis in 25 patients (34.8%), amiodarone-induced thyrotoxicosis in 19 patients (26.4%), toxic multinodular goitre in 18 (25%), excess levothyroxine replacement in 5 (6.9%) and other causes comprised the remaining 5 cases. The majority (51, 70.8%) were admitted to a cardiology service, with the remaining 29.2% being treated by a medical team.

Using the 51 patients admitted to the cardiology service, the prevalence of thyrotoxicosis within all cardiac hospitalisations was 14.4 per 10,000 admissions (95% CI 10.8, 19.0). When limited to hospitalisations for cardiac ischaemic, heart failure and tachyarrhythmia the prevalence of thyrotoxicosis was 25.0 per 10,000 admissions (95% CI 18.6, 32.9). There were no cases of thyrotoxicosis coded in the group of "other" cardiac diagnoses, which comprised 14, 944 discharges.

Patients with concurrent thyrotoxicosis were more likely to present with a tachyarrhythmia - 47 cases (65.3%), compared to heart failure (27 cases [37.5%]) or cardiac ischaemia (16 cases

[22.2%]). Mixed disease was present in 17/72 patients (≥2 diagnoses). All patients with levothyroxine over-replacement presented with a tachyarrhythmia (atrial fibrillation in four and ventricular tachycardia in one patient) and varied in severity of thyrotoxicosis with an FT_4 level up to 49 pmol/L.

Māori comprised 36.1% of those with thyrotoxicosis-associated cardiac admissions. The prevalence of thyrotoxicosis within Māori admitted with cardiac ischaemic, heart failure and tachyarrhythmia was higher than that seen in non- Māori with the same diagnoses, particularly in those under the age of 65 (overall 46.7 per 10,000 admissions vs. 20.6 per 10,000 admissions; aged 65 and under prevalence rate ratio 1.1 [95% CI 0.1, 4.5; p 0.8573]; aged over 65 prevalence rate ratio 2.3 [95%CI 1.0, 4.9; p0.0271]). Māori admitted with thyrotoxicosis-associated cardiac disease were younger than non-Māori (median age 56.5 vs. 65.5 years, p=0.003) and presented with less dysrhythmia and more cardiac failure (53.9% vs. 71.7%, p=0.126 and 57.7% vs. 26.1%, p=0.008 respectively, Figure 1). There was no difference in severity of thyrotoxicosis between Māori and non-Māori (p=0.568) unless patients with AIT were excluded. AIT accounted for 11/16 cases of severe thyrotoxicosis in non-Māori whereas Māori were no more likely to have AIT than expected for the population demographics (3/19 Māori).

Discussion

Admissions for cardiac complications of thyrotoxicosis were relatively infrequent, averaging just less than one admission per month compared to 368 monthly cardiac admissions over the same time period. Amongst admissions for cardiac conditions that were potentially thyrotoxicosis-related (cardiac ischaemia, tachyarrhythmias and heart failure) the prevalence of thyrotoxicosis was 25.0 per 10,000 admissions. Tachyarrhythmias were the most common thyrotoxicosis-associated cardiac admissions but over one-third of hyperthyroid patients admitted had heart failure and almost one-quarter experienced an acute ischaemic cardiac event. In 23.6% of patients more than one of these cardiac complications were present. Approximately one-third of the cases of thyrotoxicosis were iatrogenic with over one-quarter of the cohort having amiodarone-induced thyrotoxicosis. This is a much higher proportion of amiodarone-induced thyrotoxicosis than would normally be expected in a general thyrotoxic cohort and is likely to reflect the underlying cardiac disease in this cohort. Interestingly, while often considered relatively benign, levothyroxine over-replacement comprised almost 7% of the thyrotoxic cohort, particularly affecting older non-Māori and all had tachyarrhythmias (atrial fibrillation or ventricular tachycardia).

From this retrospective study, Māori appear to have a greater burden of disease than non-Māori when admitted with thyrotoxicosis-associated cardiac disease. Māori patients were younger when compared with non-Māori, reflective of the Māori population demographic, although there was no difference in severity of thyrotoxicosis between the two groups. In addition, the type of cardiac involvement differed between the two groups with Māori patients more commonly experiencing cardiac failure than non-Māori. This parallels the known increased rate of admissions for heart failure in Māori as compared to non-Māori [7], which was also seen within this study period.

A significant limitation of this study is that being retrospective, the reasons for the ethnic

disparity could not be identified. Possible contributors to these ethnic differences include the concepts that both the cardiac and/or thyroid disease in Māori is more severe, or that Māori have higher rates of underlying cardiac disease, such as the known higher rate of rheumatic heart disease when they develop thyrotoxicosis, or that both conditions are more prevalent. It was not clear from the notes as to the duration of thyrotoxicosis prior to presentation, treatment duration, and whether the treatment of their thyrotoxicosis was optimal. The duration of untreated disease during initial work up of thyrotoxicosis is longer in Māori than non-Māori (unpublished observations) and barriers to care in other areas have been shown to contribute to more severe presentations and outcomes for Māori [10]. In addition, there are likely social factors contributing to the discrepancy. Māori are overrepresented in lower socioeconomic deciles [11], which reduces access to medical care. It is possible that a delay in receiving treatment, or under-treatment of thyrotoxicosis may result in a higher rate of cardiac dysfunction.

This health disparity seen for Māori can also be adversely affected by other important comorbidities such as obesity, hypertension, rheumatic heart disease, metabolic syndrome and diabetes mellitus, also known to disproportionately affect Māori [12,13]. Prospective work in this area, accurately quantifying the disparity and reviewing the individual, social and healthcare factors that influence it, is needed to identify areas to make improvements.

Current recommendations are to screen for hyperthyroidism in patients with atrial fibrillation. Given the potential role of thyrotoxicosis in heart failure, and the prevalence of thyrotoxicosis, particularly in Māori, noted in this study it might be suggested that these patients should also be assessed for hyperthyroidism. As this study is retrospective and notes based, it only illustrates the hyperthyroidism that was identified and coded, not what existed, as there may have been additional patients with undiagnosed thyrotoxicosis. There is the potential to under-count thyrotoxicosis in this population, particularly in Māori if there was a bias in testing. This could be avoided with a well-designed prospective cohort study.

Interestingly, there were no cases of thyrotoxicosis in any of the other cardiac diagnoses despite this group being almost 15,000 patients and a background prevalence of thyrotoxicosis in our community of 0.2% [14]. This suggests that a significant number of cases of thyrotoxicosis were missed in these cardiac patients. This is important as not only is thyrotoxicosis very treatable, but thyrotoxicosis is also associated with an increased risk of cardiovascular mortality [15]. In addition, development of a euthyroid state should be expected to improve the cardiac status.

Conclusions

Māori are over-represented amongst patients admitted with cardiac complications of thyrotoxicosis and more often present with cardiac failure than non-Māori. Measurement of thyroid function should be considered in patients presenting not only with atrial fibrillation but patients presenting with cardiac failure, particularly if they are Māori. Further work is needed to understand this disparity, determine whether it also occurs in other indigenous populations and identify effective interventions.

Acknowledgements

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Brandt F, Green A, Hegedus L, Brix TH. A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. Eur J Endocrinol. 2011;165:491-7.

2. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344:501-9.

3. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. 2012;345:e7895.

4. Yue WS, Chong BH, Zhang XH, Liao SY, Jim MH, Kung AW, et al. Hyperthyroidism-induced left ventricular diastolic dysfunction: implication in hyperthyroidism-related heart failure. Clin Endocrinol (Oxf). 2011;74:636-43.

5. Kim DD, Young S, Cutfield R. A survey of thyroid function test abnormalities in patients presenting with atrial fibrillation and flutter to a New Zealand district hospital. N Z Med J. 2008;121:82-6.

6. Nigam P, Morton A. Are Maori women at increased risk of cardiac complications of Graves disease? N Z Med J. 2012;125:90-2.

7. Riddell T. Heart failure hospitalisations and deaths in New Zealand: patterns by deprivation and ethnicity. N Z Med J. 2004;118:U1254.

8. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European heart journal. 2010;31:2369-429.

9. Statistics New Zealand. Census quickstats about Māori. 2013 [accessed September 8, 2015]. Available from: http://www.stats.govt.nz/Census/2013-census/profile-and-summary-reports/quickstats-about-maori-english.aspx

10. Robson B, Ellison-Loschmann L. Māori and cancer care in Aotearoa/New Zealand - responses to disparities. European journal of cancer care. 2016;25:214-8.

11. Salmond C, Crampton P, King P, Waldegrave C. NZiDep: A New Zealand index of socioeconomic deprivation for individuals. Soc Sci Med. 2006;62:1474-85.

12. Milne RJ, Lennon DR, Stewart JM, vander Hoorn S, Scuffham PA. Incidence of acute rheumatic fever in New Zealand children and youth. J Paediatr Child Health. 2012;48:685-91.

13. Gentles D, Metcalf P, Dyall L, Sundborn G, Schaaf D, Black P, et al. Metabolic syndrome prevalence in a multicultural population in Auckland, New Zealand. N Z Med J. 2007;120:U2399.

14. Gibbons V, Conaglen JV, Lillis S, Naras V, Lawrenson R. Epidemiology of thyroid disease in Hamilton (New Zealand) general practice. Aust N Z J Public Health. 2008;32:421-3.

15. Giesecke P, Rosenqvist M, Frykman V, Friberg L, Wallin G, Höijer J, et al. Increased Cardiovascular Mortality and Morbidity in Patients Treated for Toxic Nodular Goiter Compared to Graves' Disease and Nontoxic Goiter. Thyroid. 2017;27:878-885.

277 **Table 1. Characteristics of patients with thyrotoxicosis-associated cardiac admissions**

Median age (range)		59.5 (23-88)	
Gender	Female	48 (66.7%)	
Ethnicity	Māori	26 (36.1%)	
	Non-Māori	46 (63.9%)	
Median length of stay (range)		5 days (0-30) - Māori 5 (1-23) - Non- Māori 5 (0-30)	p=0.6334
Thyrotoxicosis cause	Graves' disease	25 (34.8%)	
	AIT	19 (26.4%)	
	TMNG	18 (25%)	
	Thyroxine	5 (6.9%)	
	Other	5 (6.9%)	
Cardiac diagnosis[a]	Tachyarrhythmia	47/72 (65.3%) - Māori 14/26 (53.8%) - Non- Māori 33/46 (71.7%)	p=0.126[b]
	Heart failure	27/72 (37.5%) - Maori 15/26 (57.7%) - Non-Maori 12/46 (26.1%)	p=0.008[b]
	Cardiac ischaemia	16/72 (22.2%) - Maori 5/26 (19.2%) - Non-Maori 11/46 (23.9%)	p=0.646[b]
Severity of thyrotoxicosis FT_4 (RR 12-22 pmol/L)	Mild - FT_4 <30 pmol/L	28/72 (38.9%) - Māori 8/26 - Non- Māori 20/46	
	Moderate - FT4 31-50 pmol/L	17/72 (23.6%) - Māori 7/26 - Non- Māori 10/46	p=0.543
	Severe - FT4 >51 pmol/L	27/72 (37.5%) - Māori 11/26 - Non- Māori 16/46	

AIT = amiodarone-induced thyrotoxicosis; TMNG = toxic multinodular goitre; FT_4 = free thyroxine level; RR = reference range; [a]Patients may have more than one diagnosis so total adds up to more than the total number of patients. [b]Bonferroni adjustment used to recognise multiple diagnoses, $p<0.017$ used to reject the null hypothesis.

1.

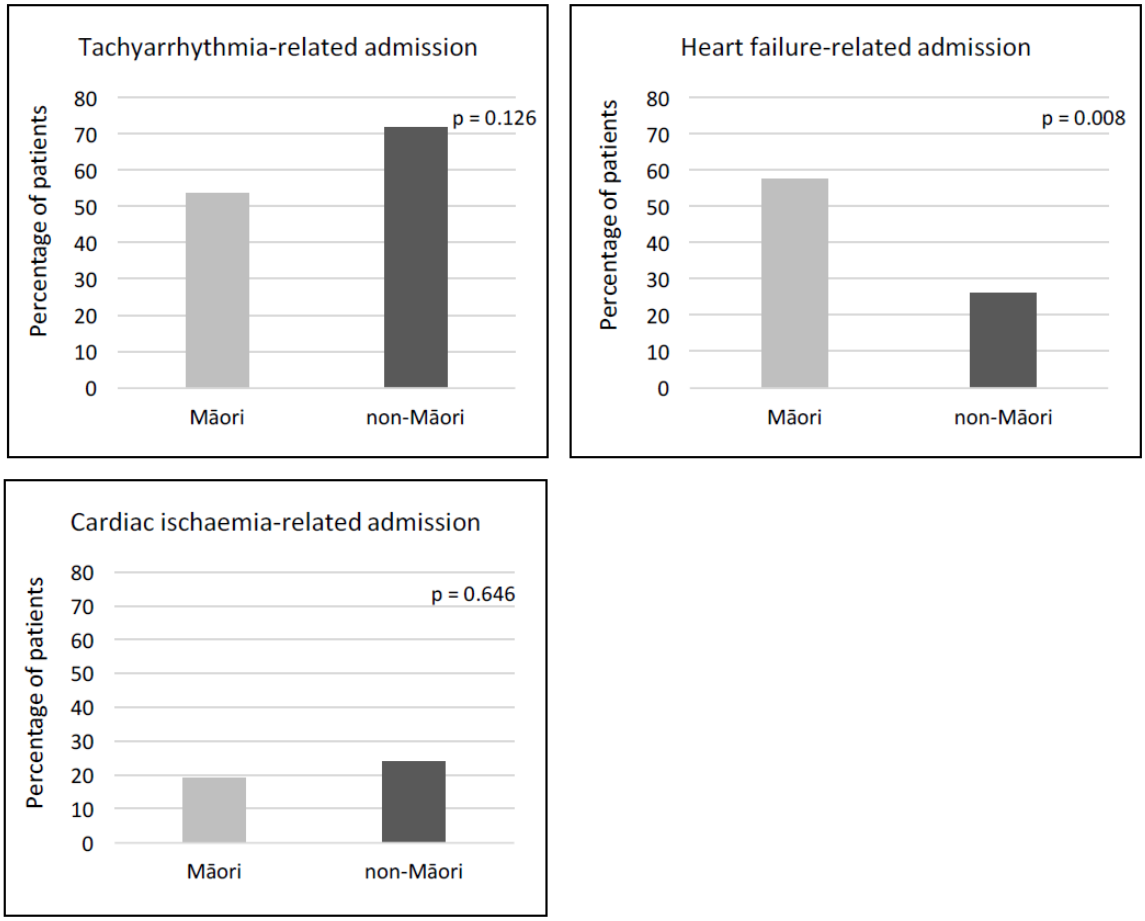

Tachyarrhythmia-related admission
Percentage of patients
80
70
60
50
40
30
20
10
0
p = 0.126
Māori
non-Māori
Heart failure-related admission
Percentage of patients
80
70
60
50
40
30
20
10
0
p = 0.008
Māori
non-Māori
Cardiac ischaemia-related admission
Percentage of patients
80
70
60
50
40
30
20
10
0
p = 0.646
Māori
non-Māori

Figure Legends

Figure 1. Percentage of patients presenting with tachyarrhythmia, heart failure or cardiac ischaemia, by ethnicity