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# Factors Influencing Prescribing of Statins in Singapore Compared to Queensland, Australia

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## Abstract

HMG-CoA reductase inhibitors (statins) are widely prescribed for dyslipidaemia with established benefits in reducing cardiovascular disease mortality and morbidity. Controversy remains surrounding statin use in low risk patients and patients of certain ethnicities. The aim of this study was to identify factors which influence the prescribing of statins by interviewing doctors from Queensland, Australia and Singapore. Purposive interviews were conducted with prescribers in Queensland Australia (n=20) and Singapore (n=21) to determine factors influencing statin prescribing. Cost, availability of generics and statin potency were major factors significantly influencing Singaporean prescribers compared to Australian prescribers ($p<0.05$). Although not significant, the potential for drug interactions also impacted statin prescribing in Singapore compared to Australia ($p=0.0516$). Cost and statin potency were major factors influencing the prescribing of statins in Singapore compared to Australia. Patients may be prescribed the cheaper, less potent statins potentially resulting in reduced patient benefits.

## Introduction

HMG-CoA reductase inhibitors (statins) are widely used to effectively reduce the cardiovascular consequences of dyslipidemia in persons with moderate and high cardiovascular risk (Wu, Zhu et al. 2013). The safety and efficacy of statins have been extensively studied in multiple large randomised controlled trials demonstrating reduced cardiovascular morbidity and mortality with statin use (Golomb and Evans 2008). This established benefit of statins in patients with cardiovascular disease has led to the extensive use of statins worldwide. In Australia, atorvastatin, rosuvastatin and simvastatin account for three of the top ten most prescribed medications. In addition, atorvastatin and rosuvastatin were the top two most costly drugs to the government with a combined cost of more than $500 million for the financial year ending July 2014 (Pharmaceutical Benefits Scheme 2014).

Statins are generally well tolerated by patients, with musculoskeletal complaints being the most commonly reported adverse effect observed in up to 25% of patients (Golomb and Evans 2008, Fernandez, Spatz et al. 2011). These musculoskeletal complaints range from commonly reported myopathies such as muscle weakness, fatigue and pain to rare~~r~~ and more serious forms such as rhabdomyolysis, which is estimated to occur in one patient per million prescriptions (Chang, Staffa et al. 2004). Intensive statin therapy (higher doses) and drug-interactions have

been suggested as possible factors influencing musculoskeletal toxicity and other adverse effects such as hepatotoxicity (occurring in 0.5-2% of statin users), new onset diabetes mellitus (which may occur in up to 6% of users, most of whom have previous features of metabolic syndrome), peripheral neuropathy and autoimmune diseases (Golomb and Evans 2008, Navarese, Buffon et al. 2013, Tierney, Thurman et al. 2013). Discrepancies between patient population between studies, as well as the strict exclusion criteria of many large-scale randomised controlled trials has meant that the reported incidence of many statin adverse effects may be lower than the true figure (Bitzur, Cohen et al. 2013). Recently, there has been increasing concern regarding their detrimental effects on cognitive function and renal toxicity, which is largely based upon case reports thus limiting our understanding of causality and incidence of these adverse events (Golomb and Evans 2008).

Adverse drug reactions, drug potency, cost, pharmaceutical marketing and patient demographics have all previously been shown to influence prescribing patterns (Nutescu, Park et al. 2005). Statins are amongst the most widely prescribed medications worldwide, so potential influences on prescribing and on the toxicity of statins is important. One suggested major consideration regarding statin toxicity is a patient's ethnic background. To date, pharmacokinetic studies have shown that individuals of Asian ethnicity have higher plasma levels of certain statins, such as rosuvastatin, when given at the same dose compared to Caucasian patients (Tan, Low et al. 2009). Whether this observation also correlates to increased risk or incidence of toxicity is unclear, although studies to date suggest no increased rate of adverse effects in Asian patients (Tan, Loh et al. 2003, Tan, Low et al. 2009, Wang and Ge 2014). As mentioned previously, whether this is truly a reflection of clinical practice or a result of strict exclusion criteria is not clear. It has been suggested that physicians often dismiss the possibility that even the most common adverse effects reported by patients may be statin-related, which is a serious cause for concern (Golomb, McGraw et al. 2007). Failure to recognise statin-induced adverse effects can potentially lead to incorrect treatment decisions, polypharmacy and compromises patient care, in particular considering the possible genetic variability and response to statin treatment between patients of different ethnic backgrounds (Golomb, McGraw et al. 2007).

**Aim of the study**

The aim of this study was to explore factors influencing the prescribing of statins in Australia. Given the uncertainty regarding the role that ethnicity plays in both therapeutic response and adverse effects, the study was expanded to include Singapore, a mainly Asian country. Factors previously shown to influence prescribing patterns such as adverse drug reactions, potency, cost, and patient demographics, formed the basis of this study.

**Methods**

Clinicians were selected as the participants for this study as to explore their knowledge of statins, awareness of adverse effects and reasoning when prescribing statins. Interviews were considered more appropriate than surveys as it enabled more flexibility and exploration of issues, is one of the main data collection tools used in qualitative research and is an effective approach to access people's perceptions, meanings, definition of situations and constructions of reality. In addition to this clinician survey response rates are traditionally quite low. Ethical approval was obtained from Griffith University Human Research Ethics Committee and the Institutional Review Board (IRB), Singapore.

**Data Collection Tool**

The questionnaire was developed around the primary objective of the project namely to explore the factors impacting clinicians' prescribing of statins. The first six questions were completed by participants themselves as these involved the collection of demographic information such as age, qualifications, years in practice, location and the age group that made up the majority of their patients. The remainder of the questions used in the interview were developed based on the literature review of factors that considered to influence drug prescribing (Nutescu, Park et al. 2005) and were open-ended to encourage participants to give as much detail in their answer and not limiting their responses. Members of the research team experienced in qualitative research were involved in development of the tool with input from a practising cardiologist. Pilot testing was conducted on the initial tool with five Australian general practitioners. The number and theme of questions remained the same but

the wording was modified to reduce leading of participants. The general practitioners involved in this initial pilot study were not included in the final study.

**Interview Sample**

Semi-structured interviews were conducted with general practitioners, general practitioner registrars, hospital registrars, and consultants. Clinicians from Australia and Singapore were selected to enable a comparison with regards to the factors that affect prescribing in these two countries.

A purposive sampling strategy was followed. This involved the identification and selection of clinicians who had experience in prescribing statins as well as covering a range of different size practices in both community and hospital settings. In Queensland, Australia, clinicians were from metropolitan and regional areas covering south (Gold Coast) and far north (Yeppoon) Queensland. As general practitioners (GPs) are the clinicians largely involved in the prescribing of statins on a regular basis the majority of Australian participants were GPs. In Singapore equal numbers of GPs and specialists were interviewed from a range of different practices throughout Singapore. The sample size was ultimately determined by the principle of saturation (Glaser, Strauss et al. 1968). A priori of 15 interviews was set with initial analysis after this time. The stopping criterion was then tested after each successive interview.

**Data Collection**

A project information pack including the interview questions was given to each participant before the interview took place. The information packs contained consent forms which participants signed before the interviews commenced. This consent form included permission for the interviews to be audio recorded. One interviewer conducted all interviews which were flexible and semi-structured with open-ended questions. No cognitive debriefing was performed. The interview procedure therefore allowed the participants to express their experiences in their own words. Thus the length of time and amount of information gained was dependent on the participant and the importance of the issue to the participant. Contextual data, for example field notes, were included to add further explanation. The audio recordings were transcribed verbatim, interview transcripts were de-identified and the audio files were destroyed once transcribed. Data was collected until data saturation was reached as defined by no new forthcoming perspectives.

**Data Analysis**

To ensure the accuracy of the transcribing the research team conducted quality checks and verified that different accents from participants were inferred correctly. The qualitative data collected was evaluated using descriptive analysis primarily as well as thematic analysis of the interviews. These were collated and trends identified were independently validated by three members of the research team in relation to the objectives of the research project with no differences between members occurring.

**Statistical Analysis**

The demographic data represents the participant's age, gender, experience, geographic location, and size of practice. Quantitative statistical analysis was conducted following the descriptive analysis of responses to compare the two sample groups, namely the Australian and Singaporean clinicians. Fisher's Exact test was used to measure the group differences and GraphPad InStat3 was used to conduct the analysis. The level of significance considered acceptable was ($P < 0.05$) with respect to the variables compared.

**Results and Discussion**

A total of 41 clinicians were interviewed: 20 in Australia and 21 in Singapore. As shown in Table 1 participant age group and experience was similar in both countries.

Participants' responses to direct questions on factors influencing prescribing of statins are shown in Table 2. Cost (81% vs. 45%) and the availability of generics (95% vs. 20%), were found to be key factors that significantly influenced prescribing in Singapore compared to Australia with one clinician stating "If they are poorer, I am more likely to use a cheaper generic". Some clinicians in Singapore went further to state that a lack of drug subsidies contributed to the cost issue saying "In Singapore unlike in Australia the patients don't get free medications so therefore their ability to pay out of pocket is a very big factor". Potency was also an important consideration in Singapore compared to Australia (86% vs. 55%) with some prescribers stating "Most of

**Table 1: Participant demographics. Data shown is the mean and standard deviation**

| | Australia | Singapore |
|---|---|---|
| **No. of clinicians** | 20 | 21 |
| **Average age (years)** | 43.4±12.4 | 43.9±9 |
| **Practising experience (years)** | 17.1±11.4 | 18.6±8.5 |
| **Clinic Size (number of practitioners)** | 7.1±2.8 | 1.4±0.9 |

**Table 2: Participants' responses on factors influencing prescribing**

| Variable | Singapore clinicians n = 21 (%) | Australian clinicians n = 20 (%) | Fisher's Exact Test |
|---|---|---|---|
| ***Is cost a factor in selection?*** | | | |
| Yes (n = 26) | 17 (81) | 9 (45) | *P* = 0.0247 |
| No (n = 15) | 4 (19) | 11 (55) | |
| ***Does the availability of generics affect prescribing?*** | | | |
| Yes (n = 24) | 20 (95) | 4 (20) | *P* < 0.0001 |
| No (n = 17) | 1 (5) | 16 (80) | |
| ***Is pharmaceutical marketing a factor?*** | | | |
| Yes (n = 15) | 7 (33) | 8 (40) | *P* = 0.7513 |
| No (n = 26) | 14 (67) | 12 (60) | |
| ***Is potency a factor taken into consideration?*** | | | |
| Yes (n = 29) | 18 (86) | 11 (55) | *P* = 0.0431 |
| No (n = 10) | 3 (14) | 9 (45) | |
| ***Are drug interactions considered when prescribing statins?*** | | | |
| Yes (n = 27) | 17 (81) | 10 (50) | *P* = 0.0516 |
| No (n = 8) | 4 (19) | 10 (50) | |
| ***Do you consider statin-induced myalgia?*** | | | |
| Yes (n = 32) | 19 (90) | 13 (65) | *P* = 0.0670 |
| No (n = 7) | 2 (10) | 7 (35) | |
| ***Are statins beneficial in patients with low cardiovascular disease risk?*** | | | |
| Yes (n = 16) | 7 (33) | 9 (45) | *P* = 0.5303 |
| No (n = 25) | 14 (67) | 11 (55) | |

my patients reach their target LDL with rosuvastatin (10 mg) whereas a lot of them do not with simvastatin (40 mg) and that's a big issue for us". While not quite significant (*P*=0.0516) the potential for drug interactions (81% vs 50%) was also a major influence in Singapore compared to Australia. Although the concern for musculoskeletal complaints was not significantly different between the two countries, 90% of prescribers in Singapore stated that it would influence them prescribing a statin. Prescribers from both countries were equally divided as to whether (33% vs. 45%) or not (67% vs. 55%) statins should be prescribed in patients with low cardiovascular risk. Similarly prescribers were equally influenced by pharmaceutical marketing.

The aim of this project was to identify the key factors that influence prescribing of statins in Australia and Singapore. Interviews were conducted with prescribers and focused on factors previously shown to influence prescribing, namely cost, potency, drug interactions, adverse drug reactions and pharmaceutical marketing. Cost, the availability of generics, and drug potency significantly influenced prescribers in Singapore compared to Australia.

The two countries have different drug subsidy schemes which could explain these differences. In Australia the Pharmaceutical Benefits Scheme (PBS) subsidises individual drug costs and patients mainly contribute a co-payment towards their medicine (PBS 2013). Currently this base co-payment is approximately $37 per month's supply per item with a possible premium applied for certain brands. Under the PBS the price of the different generic statins would be the same for a patient regardless of the statin with the price increasing for non-generic brands by around $3. Thus the choice of statin and availability of generics does not greatly influence the cost to the patient under the Australian PBS. In comparison, Singapore does not have a specific drug subsidy scheme but rather uses a savings scheme based on income. Therefore, the price to the patient is dependent on the actual price of the statin which varies considerably between drugs. For example, a month's supply of simvastatin 10 mg would be $60 whereas rosuvastatin 10 mg would be approximately $90. Given these differences it is not surprising that cost is a major factor in Singapore. The availability of generics further influences these prices, reducing the cost to the patient. In Singapore the costs for different generic statins can vary by up to $50 per month. Given this additional cost to the patient, it is understandable that both cost and generic availability is a more influential factor in Singapore.

Potency was another factor of significant difference between prescribers in Australia and Singapore. Similarly drug interactions were another important consideration, particularly in Singapore. Several studies in Asian populations have shown that patients receiving low to medium potency statins did not achieve their target low density lipoprotein (LDL)-cholesterol levels but those on higher potency statins were more likely to achieve these targets (Ho, Chin et al. 2006). Given the uncertainty regarding the influence of ethnicity on statin efficacy and toxicity, it is possible that prescribers in Singapore are more cautious when prescribing statins. This may also explain the higher percentage of prescribers in Singapore (90% vs 65% which is not statistically different) stating that the concern regarding musculoskeletal complaints influences their prescribing. However, this increased concern regarding statin toxicity in Asian patients is largely unfounded as several recent studies have shown no differences in statin toxicity between Asian and Caucasian patients.

Pharmaceutical marketing and reputation of drug companies have been long considered to have a major impact on prescribers. However, we found that prescribers from both countries indicated that they were essentially not affected by marketing. Although not statistically significant, it is of particular concern that several clinicians in both countries would consider prescribing statins to patient with low cardiovascular risk. Given the increased spotlight on the use and safety of these drugs this needs to be investigated further.

## Conclusion

In conclusion, the findings from this preliminary work show that cost, availability of generics and drug potency are the key factors that significantly influence prescribing of statins in Singapore compared to Australia. Drug interactions and the potential for musculoskeletal effects were considered by both countries but by a higher percentage of Singapore prescribers. Further investigation of the possible impact on patient outcomes due to prescribing of the cheaper, less potent statins in Singapore is required.

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