Opportunities Tapped into the

Regional Variance of Drug-Use Practices in Japan

A close look at the variations in therapeutic practices by Prefectures and Regions of Japan for a select Therapeutic Categories, and underlining some likely fresh avenues of therapeutic practices optimization and socio-economic savings.

Research Category

Special Report

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DISCLIMAER : All data presented herein are from the sales data from Wholesalers only. This may miss some data points generated through direct sales channels.

Background & Rationale

Japan has one of the most developed healthcare systems in the world and it is commonly believed that the overall medical infrastructure and practices are evenly spread across the nation at large. There also exist a number of highly respected 'therapy/disease focused associations' in Japan, which keep track of scientific developments into their respective fields and issue therapy guidelines periodically. On ground however, significant levels of variations in medical practices actually exist across the nation.

In this, perhaps the first ever study of its kind – Encise Research Center (ERC) attempts to accumulate some vital data points from a few selected therapeutic categories to present a picture of how therapy paradigm (or drug use practices) varies among Japanese prefectures and regions.

The purpose of the study is to look into a relatively less explored area of variations into drug use practices by geographic regions and present a landscape of some factual ground scenarios on a rather less-closely looked aspect. ERC does not give any conclusion or guidance and leaves it completely on the readers on how they want to interpret and use the findings.

When the available drug regimens are very similar in their pharmacological profile (indication, efficacy, safety etc.) for a desired therapeutic outcome, the selection of a drug largely depends on the choice of the prescribers. However, there could be many factors working behind making such choices. In general – the standard marketing-mix of 'Four Ps' (i.e. Promotion, Price, Product, and Place) could be extended with two more 'Ps' in case of pharmaceutical products to define these factors, are – Prescriber (who makes the choice) and Patient (fitness to the drug regimens, based on his/her biologic and socio-economic profile).

The output of these 'Six Ps' also reflects into the sales pattern of new vs. conventional drugs of closely related pharmacological profiles. Whenever a pharmaceutical product goes off-patent, the promotional thrust on it falls, and the generic versions debut to take the market-share. On the other hand, while a new drug comes (or if comparable patented drug still exists) addressing the similar therapeutic need, but

with much more promotional efforts – it continues to generate sales.

Hence, while the sales of a pharmaceutical product is very much proportional to the promotional efforts (for similar pharmacological profile drugs), it may also have some socio-economic implications (or burdens). New drugs do not always mean the superiority to the conventional, existing options, and this notion could be easily validated by seeing the practice pattern of some prescribers who prefer to use conventional options to get desired therapeutic outcome.

On a wider geographic canvas – these factors also contribute to the variations of the drug-uses practices among regions and prefectures. Taking a closer look and presenting a broader landscape of prevailing contrasts of drug-use practices among similar drugs by prefectures and regions is the objective of this report.

We do understand that variations in drug-use practices may also depend on several factors other than promotional inputs, for instance – migration of patients, regional socio-economic conditions, variations into genetic make-up, dispersion pattern of healthcare infrastructure etc.

We also note, that advancements into the science and technologies have offered better understandings of challenges associated with conventional drugs, and also the understandings of addressing these inefficiencies. However, lack of awareness inhibits the society from benefiting itself from those understandings.

Methodology: Per capita spending (PCS) for select drug-categories was studied for prefectures and regions in comparison to their national average per capita spending (NA-PCS) in this report.

Executive Summery

Variation in drug-use practices by geographic regions is a known fact, and pharmaceutical companies study it closely for their individual product's sales & marketing intents. However, on a broader landscape how the preferences in making drug choices for a given therapeutic class vary among geographic areas, is relatively still less explored field. A better understanding of how these preferences vary with regions may provide several important understandings – they may help in optimization of therapeutic practices, may unfold some new avenues of healthcare savings and bring several other fresh perspectives to be further looked upon.

In this, perhaps the first ever report of its kind – Encise Research Center (ERC) accumulates some vital data points from a few selected therapeutic categories and presents a landscape of how therapy paradigm (or drug use practices) varies among Japanese prefectures and regions.

A few therapeutic categories were selected, and the drug groups within them identified for a comparative study. These groups were then studied for their 'per capita spending' trends by regions and prefectures. The rationale of segregating the drug groups for comparison and a quick finding on each of them are given below followed by the summary of the accumulated data-points in Table 1 and Table 2. Details are given in the following sections of this report.

Anti-osteoporosis Drugs: Oral Selective Estrogen Receptor Modulators (SERMs) and Bisphosphonates (together mentioned as S+B hereafter) are the early stage drugs (excluding vitamin derivatives, supplements etc.). They are time-tested for their safety and efficacy and they are economical. As the disease progress (falling Bone Mass Density [BMD] isn't controlled and risk/incidence of fracture increased) there is a need to Rx advanced drug – biologics and/or parathyroid hormonal preparations (M+PTH). At this point the cost of therapy sharply rises multifold. The per capita spending of the two broader drug categories were studied by prefectures and regions.

- **Findings:** **Hokkaido** region has the highest per capita spending on S+B (16% higher than national average), while **Kanto** has the lowest (-10% to the national average). **Tohoku** has the highest difference between the per capita spending patterns for the two categories (15% higher for S+B while 2% lower for M+PTH than the respective national averages).

The findings suggest a drastic variation in drug use practices among the two broader categories. While the time to switch from S+B to M+PTH largely depends on disease progression stage and the medical need, it also depends on physician's sentiments and personal choice. Considering the huge cost difference between the two categories, optimization of drugs use pattern may result into better control of osteoporosis as well as in improving economic burden on society.

Anticoagulants: Direct Oral Anti-Coagulants (DOACs) have largely replaced conventional Vitamin-K-antagonist (VKA) Warfarin and Heparins due to their ability to overcome several inefficiencies with conventional drugs. However, novel drugs are also not completely free from the issues and advancements in scientific understandings facilitate overcoming most of the inefficiencies of conventional drugs, on the other hand. Many doctors still prefer conventional options. The above two categories were compared for their per capita spending pattern by regions and prefectures.

- **Findings:** **Tohoku** region has the highest per capita spending on DOACs (38% higher than national average), while **Kinki** region has the lowest (-9% to the national average). **Akita** prefecture has the highest difference between the per capita spending pattern for the two categories (77% higher for DOACs while 11% lesser for conventional anticoagulants than their respective national averages).

Findings demonstrate that some regions and prefectures significantly prefer conventional anti-coagulants over DOACs, despite being heavily marketed to the doctors. These findings call for further investigation – if a number of doctors have learned to use conventional drugs more effectively with the help of new scientific understanding and aids, the knowledge must utilized.

Anti-hypertensive Drugs: Angiotensin II receptor blockers (ARBs) and their combinations are considered most popular antihypertensive. Many of them are still in their patent period and subject to promotional thrust. On the other hand, the group of conventional

anti-hypertensives is much economical and they continue to maintain high volume use in Japan. These include Ca-channel blockers, beta blockers, ACE inhibitors and their combinations. The above two closely related groups of drugs were studied for their geographic per capita spending pattern.

- **Findings:** **Shikoku** region has the highest per capita spending of ARB (21% higher than national average), while **Kanto** has the lowest (-6% to the national average). **Nara** prefecture has the highest difference between the per capita spending pattern for the two categories (4% less for ARB while 28% higher for the others than their respective national averages).

Like the variations in drug-use practices in the first two therapeutic categories, anti-hypertensives also provide an opportunity of further investigations for drug use optimization and to avail health benefits and economic efficiency.

Table 1
Percentage (%) Difference in 'Per Capita Spending' of the Selected Therapeutic Categories in Prefectures of Japan Compared to their National Average Per Capita Spending

		Top 3	Bottom 3	Maximum Difference	Lowest Difference
Osteoporosis	S+B	Akita (51%) Kochi (41%) Oita (38%)	Okinawa (-30%) Shiga (-23%) Saitama (-16%)	Kagawa (-5% vs 33%) Yamagata (6% vs -30%) Miyazaki (-7% vs. 21%)	Kagoshima (5% each) Miyagi (-5% vs -6%) Wakayama (17% vs 16%)
	M+PTH	Yamanashi (40%) Akita (34%) Kagawa (33%)	Okinawa (-42%) Yamagata (-30%) Shiga (-30%)		
Anticoagulants	DOACs	Akita (77%) Aomori (55%) Yamagata (50%)	Okinawa (-43%) Aichi(-26%) Mie (-17%)	Akita (77% vs. -11%) Okinawa (-43% vs. 32%) Yamagata (50% vs -8%)	Chiba (-2% vs 2%) Wakayama (-1% vs 0%) Kagawa (-1% vs 2%)
	Others	Okayama (41%) Fukui (34%) Okinawa (32%)	Aichi (-27%) Saga (-24%) Fukuoka (-5%)		
Anti-hypertensive	ARBs	Akita (51%) Kochi (36%) Fukushima (27%)	Okinawa (-27%) Shiga (-12%) Kanagawa (-12%)	Nara (-4% vs 28%) Kagoshima (2% vs -23%) Kochi (36% vs 15%	Gifu (0% vs 1%) Okayama (-1% vs 1%) Nagano (-1% vs -1%)
	Others	Akita (43%) Tokushima (29%) Nara (28%)	Okinawa (-27%) Kagoshima (-23%) Saga (-22%)		

Osteoporosis:
S+B: SERMs + Bisphosphonates
M+PTH: MAb+ Parathyroid Hormonal Preparations
Anticoagulants:
DOACs: Direct Oral Anti-Coagulants
Others: Vitamin-K Antagonist (VKA) Warfarin, Heparins
Anti-hypertensives:
ARB: Angiotensin II Receptor Blockers (and their combination formulations)
Others: Beta blockers, Ca channel blockers, ACE inhibitors (and their combination formulations)

Top 3: the top three prefectures with the highest 'per capita spending' as percentage difference from National Average Per Capita Spending for the selected drug classes.
Bottom 3: the bottom three prefectures with the lowest 'per capita spending' as percentage difference from National Average Per Capita Spending for the selected drug classes.
Maximum Difference: between the selected two drug classes from the same therapeutic class.
Minimum Difference: between the selected two drug classes from the same therapeutic class.

Source: Encise Research Center, Encise Inc.

Table 2
Percentage (%) Difference in 'Per Capita Spending' of the Selected Therapeutic Categories in Regions of Japan Compared to their National Average Per Capita Spending

		Top 2	Bottom 2	Maximum Difference	Lowest Difference
Osteoporosis	S+B	Hokkaido (16%) Tohoku (15%)	Kanto (-10%) Chubu (-2%)	Tohoku (15% vs -2%)	Chubu (-2% vs 2%)
	M+PTH	Shikoku (13%) Kinki (8%)	Kanto (-5%) Kyushu & Okinawa (-3%)		
Anticoagulants	DOACs	Tohoku (38%) Hokkaido (25%)	Kinki(-9%) Kanto (-4%)	Tohoku (38% vs 8%)	Shikoku (-1% vs 1%)
	Others	Hokkaido (29%) Chugoku (12%)	Kinki (-8%) Kyushu & Okinawa (-8%)		
Anti-hypertensive	ARBs	Shikoku (21%) Tohoku (20%)	Kanto (-6%) Kyushu & Okinawa (-2%)	Kyushu & Okinawa (-1% vs -12%)	Chubu (-1% vs -3%)
	Others	Shikoku (15%) Tohoku (11%)	Kyushu & Okinawa (-11%) Kanto (-3%)		

Osteoporosis:
S+B: SERMs + Bisphosphonates
M+PTH: MAb+ Parathyroid Hormonal Preparations
Anticoagulants:
DOACs: Direct Oral Anti-Coagulants
Others: Vitamin-K Antagonist (VKA) Warfarin, Heparins
Anti-hypertensives:
ARB: Angiotensin II Receptor Blockers (and their combination formulations)
Others: Beta blockers, Ca channel blockers, ACE inhibitors (and their combination formulations)

Top 2: the top two regions with the highest 'per capita spending' as percentage difference from National Average Per Capita Spending for the selected drug classes.
Bottom 2: the bottom two regions with the lowest 'per capita spending' as percentage difference from National Average Per Capita Spending for the selected drug classes.
Maximum Difference: between the selected two drug classes from the same therapeutic class.
Minimum Difference: between the selected two drug classes from the same therapeutic class.

Source: Encise Research Center, Encise Inc.

Variance in Therapeutic Practices by Regions & Prefectures

Anti-Osteoporosis | Anti-Coagulants | Anti-Hypertensives

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Overview of Osteoporosis Statistics in Japan: The 'Japanese Osteoporosis Society' estimates that the number of osteoporosis patients (of age 40 or over) in Japan is 12.8 million (3 million men, and 9.8 million women), which is about 10% of the population! While the measurement criteria for defining osteoporosis may vary, this prevalence rate is still extremely high compared to the USA or European countries.

The treatment goal of osteoporosis is to maintain the good skeletal (by controlling the Bone Mass Density [BMD] decay) and to reduce the incidences/ possibilities of fractures (hip and spinal are of major concern). The treatment guidelines involve a wide category or recommendations including – maintaining healthy lifestyle (especially exercising, walking etc.), giving natural supplements (vitamin D and K derivatives for instance) and a long-term drug intervention.

The drug regimen of osteoporosis can be broadly defined in 4 categories (SERMs, bisphosphonates, anti RANKL antibodies and parathyroid hormonal preparations [PTH]) – The SERMs and the bisphosphonates are considered as the initial candidates for maintaining and improving the BMD. Most of these drugs are time-tested for proven efficacy and established safety. Most of the drugs have also gone off-patent and available at low price.

As the disease progress or the need of advanced medical intervention is sought – the next stage of medication involves Anti-RANKL MAb and PTH. However, the cost of these drugs is multifold compared to oral SERMs or bisphosphonates which are generally used at early stage. More importantly, the new drugs (e.g. Romosozumab) in the pipeline for osteoporosis – which are also aimed at late stage use, are estimated to be similar or even more expensive than parathyroid hormonal preparations.

As the disease progresses, physicians have to move to advanced medicalizations, which are significantly more expensive. However, there are several factors, including the doctors' choice of 'time to switch'. It is noted in several studies that education, guidance and consultation, improving drug adherence etc., may have significant

impact on progression of disease as well as delaying the time to switch to the advanced drug.

Existing Therapy Paradigm and their Economics: Oral SERMs and bisphosphonates are the early stage drugs (excluding vitamin derivatives, supplements etc.). They are time-tested for their safety and efficacy and they are economical. As the disease progress (falling BMD isn't controlled and risk/incidence of fracture increased) there is need to Rx advanced drug – biologics and/or PTH. At this point the cost of therapy sharply rises multifold.

- ERC estimates that moving one patient from conventional oral medication to advanced drugs (e.g. PTH) costs up to about half a million JPY additional each patient/annually. 1000 patients moving to PTH bring about ¥500 million additional annual burden to the society (*PTH hormones are generally Rx once only in lifetime for 1.5 to 2 years duration only*).
- When above figures are seen into the context of osteoporosis statistics of Japan (about 12 million existing cases) and rapidly growing proportion of elderly population – the economic significance of moving patients to the advanced drugs is high.

It is also important to mention here that significant research is going on in the direction of treating osteoporosis by the means of many novel methodologies. These include – regenerative, stem-cell based therapies, development of effective biomarkers, technique of 'fill-in materials' in porous bones, 3D printings etc. There are no reasons not to hope that the issue to osteoporosis and other skeletal related challenges would be almost completely conquered in our lifetimes.

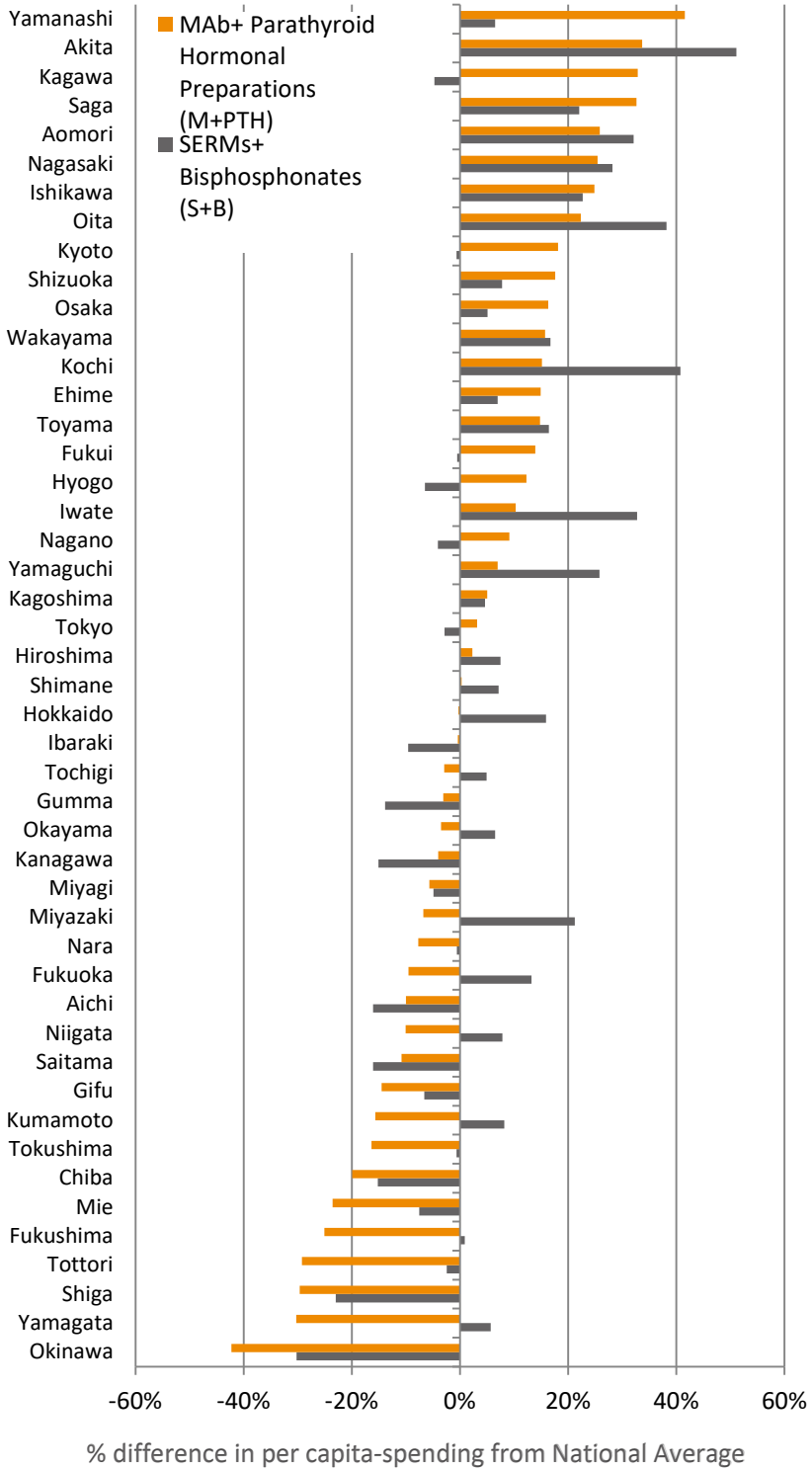
Regional Variance in Therapeutic Practices for Osteoporosis drugs in Japan:

We looked at the per capita spending by prefectures and by regions for the two drugs categories – **1.) SERMs + Bisphosphonates (S+B),** and **2.) Anti-RANKL MAb + Parathyroid Hormonal Preparations (M+PTH)**. We then compared their per capita spending from the national average per capita spending (as percent [%] difference from national average) within the same group and with each-others as shown in the Chart 1. & 2.

Prefectural Observations:

- **Akita** has the highest per capita spending on S+B (51% higher than the national average per capita spending on S+B), followed by **Kochi** and **Oita** (41% and 38% respectively on the same parameter).
- **Yamanashi** has the highest per capita spending on M+PTH (40% higher than the national average per capita spending on M+PTH), followed by **Akita** and **Kagawa** (34%% and 33% respectively).
- The maximum contrast in per capita spending between the two groups from their national average per capita spending was observed in **Kagawa** (-5% vs. 33%) followed by **Yamagata** (6% vs. -30%) and **Miyazaki** (21% vs. -7%).
- The maximum similarity in per capita spending pattern for S+B and M+PTH was observed in **Kagoshima** (5% each followed by **Miyagi** (-5% vs. -6%) and **Wakayama** (17% vs. 16%).

Chart 1.
Variance in Osteoporosis Drug Regimen Spending by Prefecture

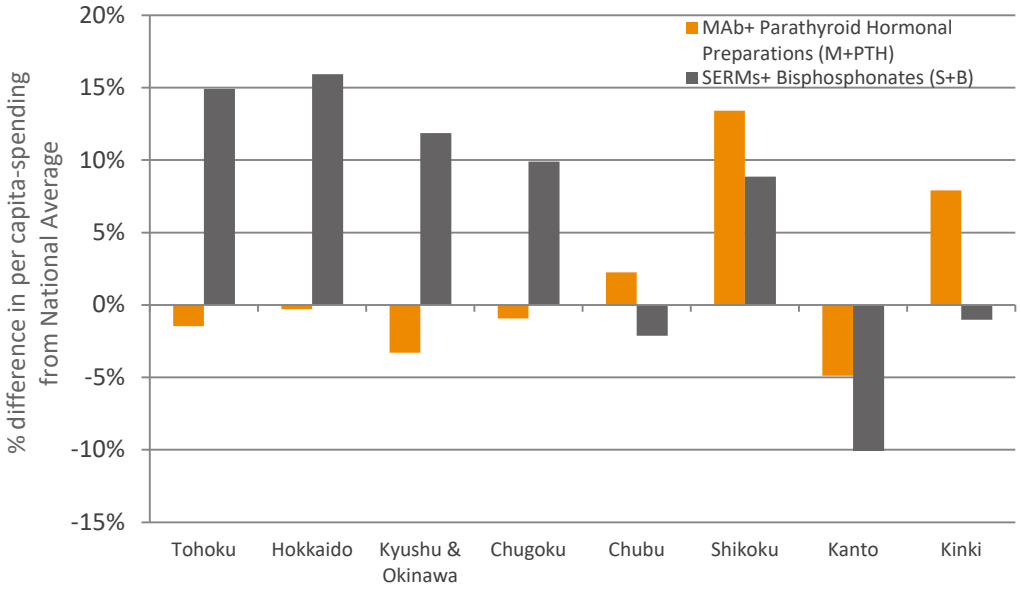


Source: Encise Research Center, Encise Inc.

Regional Observations:

- **Shikoku** has the highest per capita combined spending on S+B and M+PTH (vs. national average per capita spending) – 9% and 13% respectively while **Kanto** has the lowest use on same parameter (-10% and -5% respectively).
- **Tohoku** has the highest contrast (15% vs. -2%) while **Chubu** has the minimum contrast (-2% vs. 2%) between the spending patterns of the two broader drug categories.

Chart 2.
Variance in Osteoporosis Drug Regimen Spending by Region



Source: Encise Research Center, Encise Inc.

'Antithrombotics' are among leading therapeutic classes in Japan (5th largest in FY 03/2018 with ¥385 Billion sales and about 4%+ YoY growth). The therapeutic category's sale has seen a tremendous spur in the past few years after introduction of novel direct-acting oral anticoagulants (DOACs).

Until then, Vitamin-K-antagonists (VKA) since their introduction about 70 years ago, and heparins have been used as gold standard anticoagulants for prevention and treatment of thrombosis.

The Caveats of Conventional Anti-coagulants & the Emergence of Novel DOACs:

The primary challenge with conventional anti-coagulants VKA, warfarin is that it has a long half-life and very narrow therapeutic window. Hence, it may lead to bleedings (because of a risk of over-anticoagulation) or thrombosis (because of a risk of under-anticoagulation). To address this they require a constant monitoring.

New oral anticoagulants on the other hand offered great benefits both to the patients and physicians by getting rid of the requirements of constant laboratory monitoring and frequent controls of warfarin, without loss of their efficacy and safety.

DOACs have largely replaced warfarin due to its superior safety profile. Their half-life is also shorter, providing benefit of making 'anticoagulation bridging' unnecessary before surgery.

Though DOACs can be given orally and they are known for their superior safety profile and ease of monitoring, they are not completely free from 'issues' and they are economically much expensive. Also, some pharmacokinetic and pharmacodynamic interactions are still needed to be watched out for them.

Also, while DOACs do not require to have monitoring but they are sensitive to changes in renal function and hence are often lead to poor drug-compliance.

Conventional Anti-coagulants in the light of New Developments & Understandings:

- With the overall advancement in science and technology, the treatment surveillance methods are also improved significantly by introduction of International Normalized Ratio (INR) and self-monitoring/management methods over the years. The new technologies address the issues of monitoring challenge.
- The medical science has also developed effective strategies to address the issues of the occurrence of fresh thrombotic events with the conventional agents.
- It is also important to note that effective methods of reversing anticoagulant effect of conventional anticoagulants exist.
- The issues of sensitivity and resistance with warfarin have also been understood better during recent years.
- It is also noted in some studies that the issue of sensitivity can be addressed by using a simple genotype guidance for identification and adaptation or home monitoring. These strategies can ensure high quality therapeutic achievements. These adjustments could make warfarin the preferred drug for most people and would reduce the dramatic rise in health service expenditure.

Some recently published study in a peer reviewed journal[1] remarks that '*there are good grounds to believe that DOACs are not always superior to warfarin in routine practices particularly with an older population*'.

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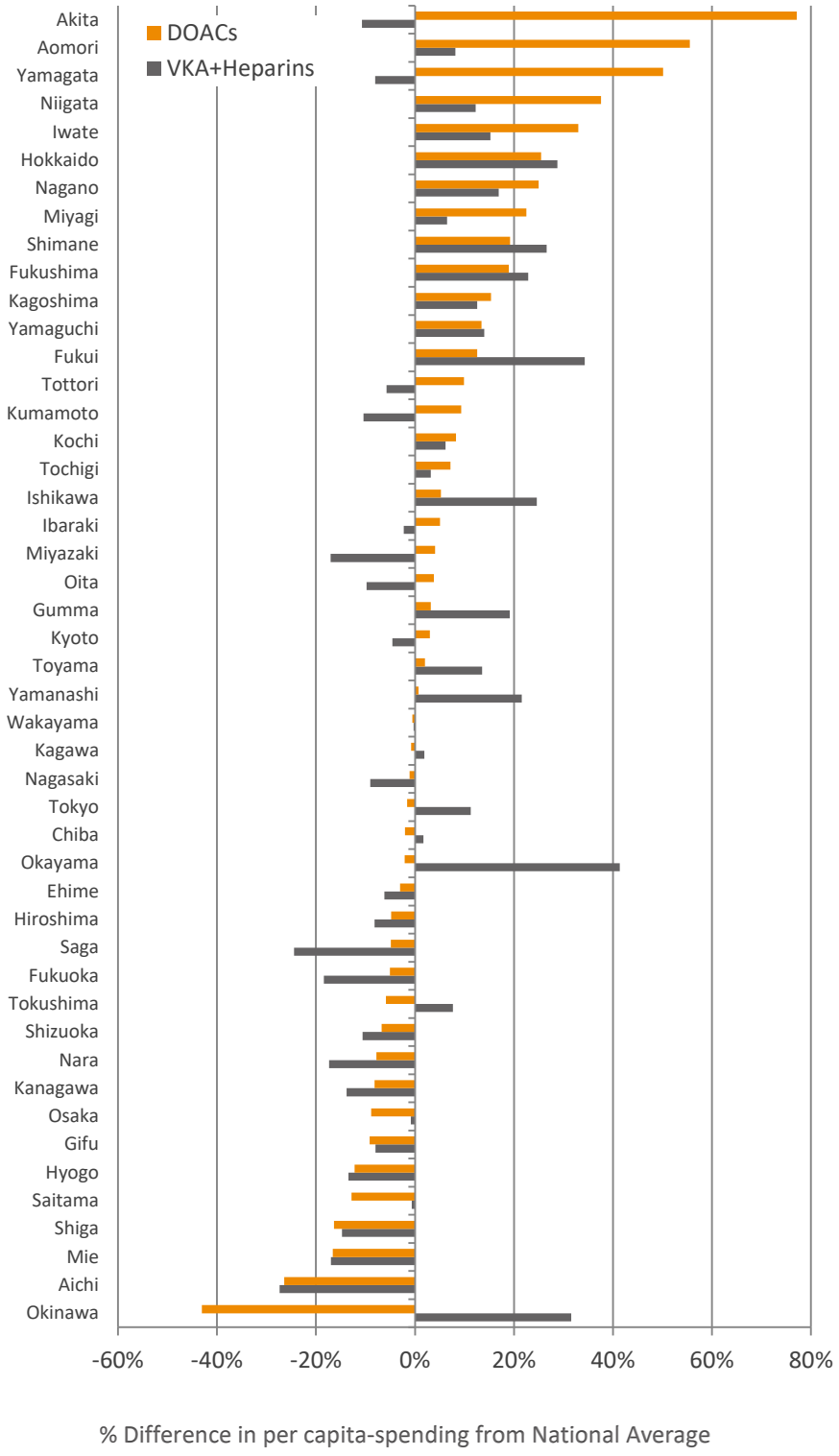
[1] Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old?. *Open Heart* 2018;**5**:e000712. doi:10.1136/openhrt-2017-000712

Observation by prefecture:

- **Akita** has the highest per capita spending on DOACs, 77% higher than the national average per capita spending on DOACs, followed by **Aomori** (55%) and **Yamagata** (50%). On the other hand, **Okinawa** has the lowest spending on DOACs on the same parameter (-43%), followed by **Aichi** (-26%) and **Mie** (-17%).
- **Okayama** has the highest per capita spending on VKA+Heparins, 41% higher than the national average per capita spending on VKA+Heparins, followed by **Fukui** (34%) and **Okinawa** (32%). While, **Aichi** has the lowest spending on VKA+Heparins on the same parameter (-27%), followed by **Saga** (-24%) and **Fukuoka** (-18%).
- The maximum difference in per capita drug spending pattern was observed for **Akita** (with 77% higher than national average per capita spending for DOACs, while 11% lesser for VKA+Heparins), followed by **Okinawa** (-43% and 32% respectively), and **Yamagata** (50% vs. 8% respectively).
- The minimum contrast in per capita drug spending pattern was observed for **Chiba** (with 2% lesser than national average per capita spending for DOACs, while 2% higher for VKA+Heparins), followed by **Wakayama** (-1% and 0%), and **Kagawa** (-1% and 2% respectively).

Chart 3.
Variance in DOACs & 'Conventional Anticoagulants' Spending by Prefecture

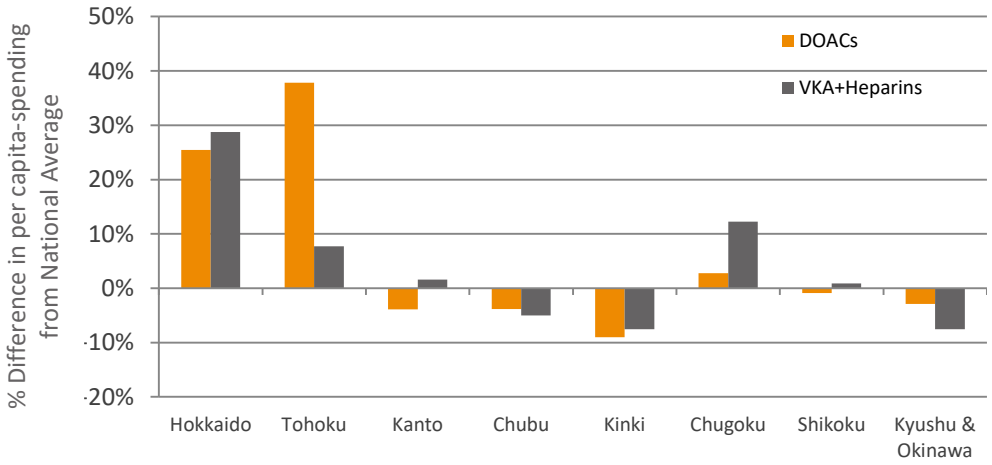


Source: Encise Research Center, Encise Inc.

Region wise variations:

- **Tohoku** has the highest per capita spending on DOACs (38% higher than the national average), followed by **Hokkaido** (25% higher on same measure). While **Kinki** has the minimum use of DOACs (-9% compared to national average per capita DOACs spending), followed by **Kanto** (-4% on same measure).
- **Hokkaido** has the highest per capita spending on VKA+Heparins (29% higher than the national average), followed by **Chugoku** (12% higher on same measure). While **Kinki** has the minimum use of 'VKA+Heparins' (-8%, compared to the national average per capita VKA+Heparins spending), followed by **Kyushu & Okinawa** (-8% on same measure).
- The minimum difference in per capita spending from national average for DOACs and VKA+Heparins was observed for **Shikoku** (-1% and 1% respectively) and the maximum difference on same major was for **Tohoku** (38%, and 8% respectively).

Chart 4.
Variance in DOACs & 'Conventional Anticoagulants' Spending by Region

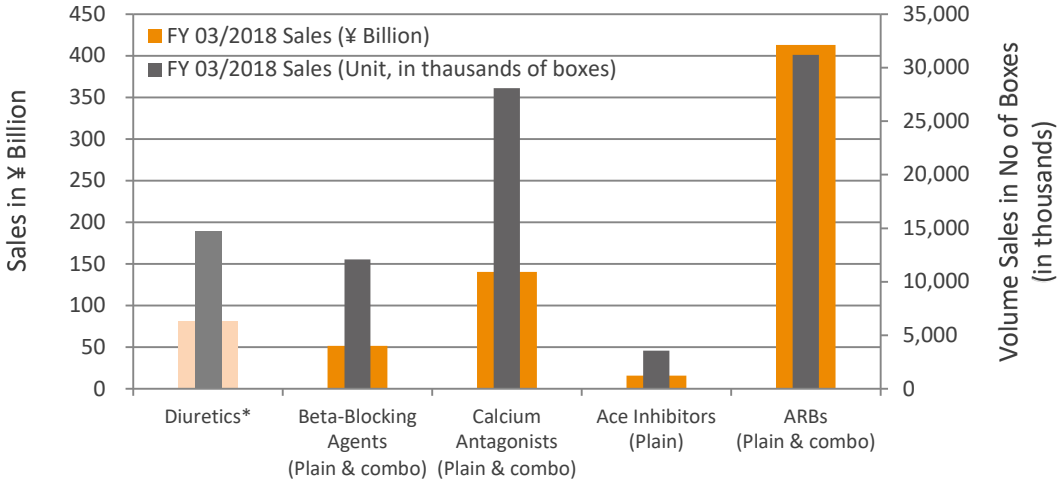


Source: Encise Research Center, Encise Inc.

As a broader therapeutic class, the drugs working on cardiovascular system form the second largest pie of Japan pharma with about 13.7% of the total sales (*the largest being the 'Antineoplastic and immunomodulating agents' which form >17% of Japan pharma sales*).

A large number of drugs are used to treat hypertension. The market, however, is dominated by four main classes. These are the beta-blockers, calcium antagonists, ACE inhibitors and angiotensin II receptor blockers (ARBs). Although each of these classes can be used alone as monotherapy, combination regimens are usually required to achieve adequate control. A quick overview of each of these key classes is given below along with their FY 03/2018 value and volume sales:

Chart 5.
Japan Anti-Hypertensive Market in FY 03/2018 (Value & Volume)



* Not included in the analysis
Source: Encise Research Center, Encise Inc.

Beta blockers: Beta blockers are the oldest (discovered in 1960s) of major anti-hypertensive classes and are largely genericized. Despite the fact that they have been exposed to a long duration of price-cuts and generics competition, they are still posting the highest volume

growth (about 2.8% YoY in FY 03/2018) among the all four anti-hypertensive drug categories.

Calcium antagonists: Calcium is an important element for muscle contraction, and basically, Ca-antagonists exert their effect by preventing the inflow of Ca via Ca-channels in heart and vascular tissue. As a result they lessen the strength of the heart's contraction and vascular constriction both. Hence they can also be used for angina. Though the class is dominated by the long-listed products (LLPs) and generics, they are (together with their combination formulations) the second largest anti-hypertensive class after ARBs and still growing by volume (FY 03/2018 sales ¥140 Billion, -4.5% YoY by value and +1.2% YoY by volume).

Angiotensin-Converting Enzyme (ACE) inhibitors: They are the earliest class of drugs to act on the renin-angiotensin system, and they had a major limitation of 'dry cough', which was effectively addressed by next generation drugs working on the same system i.e. ARBs. ACE inhibitors still post about ¥16 Billion sales but they are de-growing both by value and volume.

Angiotensin II receptor antagonists (ARBs): Like ACE inhibitors, they also act on the renin-angiotensin system but do not cause dry cough. Despite the fact that ARBs have been exposed to several special price cuts (in double digits) in recent years, they, including their combination products, posted ¥413 Billion in sales in FY 03/2018 (-12.5% YoY). The ARBs market is de-growing by value (-12.5% YoY in FY 03/2018), largely due to some patent expiries and price cuts, they are expected to fall further as major brands will go off-patent in the next couple of years. However, they are still growing on volume basis (about 2.7% YoY in FY 03/2018).

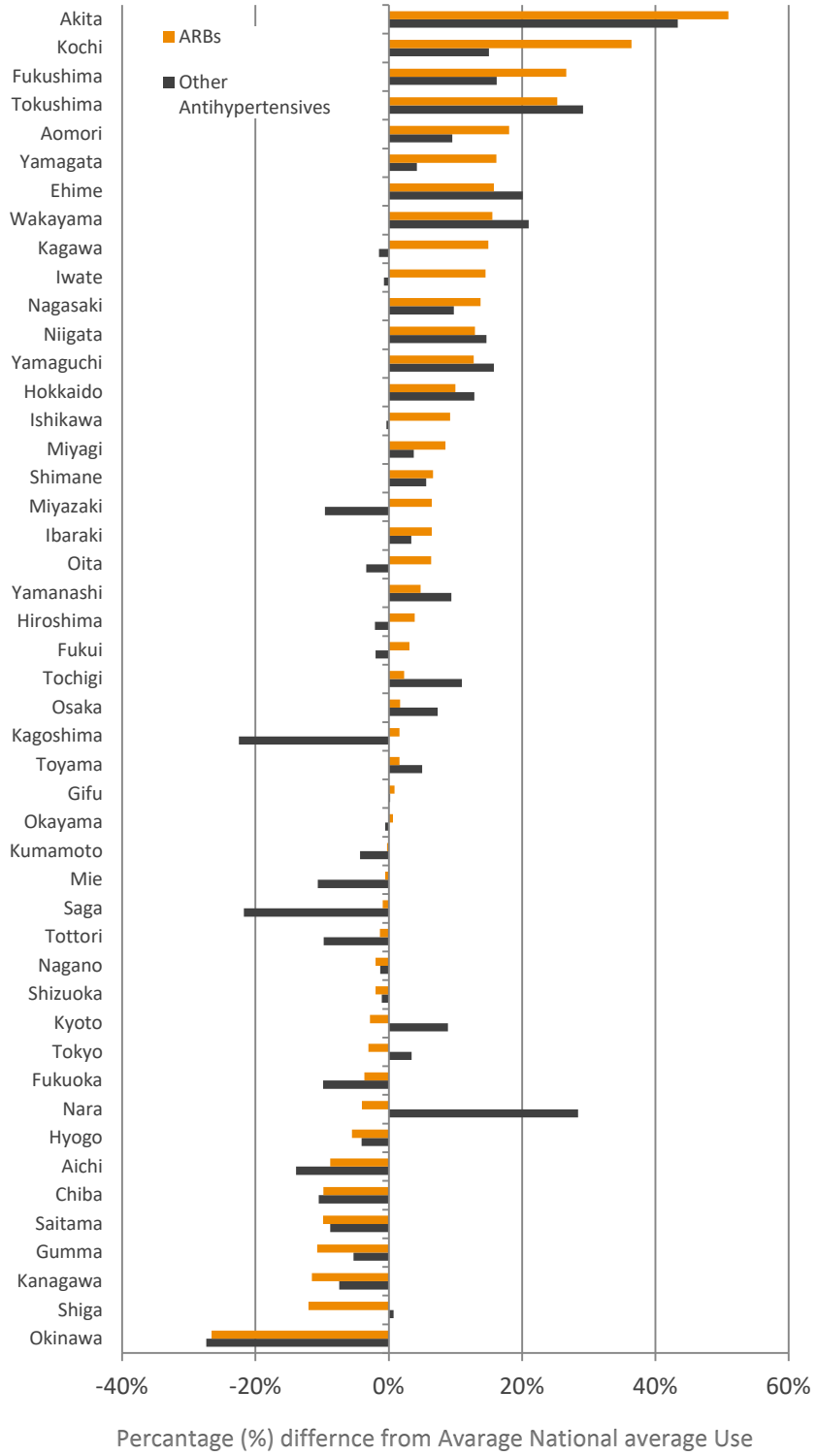
Diuretics: Specifically thiazide diuretics increase the amount of urine excreted, thereby reducing the pressure of blood filling the heart. They are mostly used in combination with other anti-hypertensives. *(A large proportion of their sales shown in the chart 5 (i.e. >60%) is contributed by Samsca (tolvaptan) alone, which is mainly indicated for hyponatremia, hence diuretics alone are not included in this analysis of anti-hypertensives).*

Observations & Findings

Variations in ARBs and other anti-hypertensives by Prefectures:

- **Akita** has the highest per capita use of ARBs (51% higher than the national average), followed by **Kochi** and **Fukushima** (36% and 27% respectively). The three prefectures also have higher per capita use of other anti-hypertensives as well (43%, 15% and 16% higher than the national average).
- **Okinawa** has the lowest per capita use of ARBs (-27% than the national average), followed by **Shiga** and **Kanagawa** (-12% for both). **Okinawa** also has overall lowest per capita use of anti-hypertensives.
- **Nara** uses less than national average for ARB (-4%) while 28% higher for other anti-hypertensives. Similar contrast is observed with **Kagoshima** (ARB 2% higher but others -23% lesser), and **Kagawa** (ARB 15% height while others -1% lower), **Miyazaki** (ARBs 6% higher while Others 10% lower).

Chart 6.
Per Capita Sepnding on ARBs and Other Anti-hypertensives by Prefecture

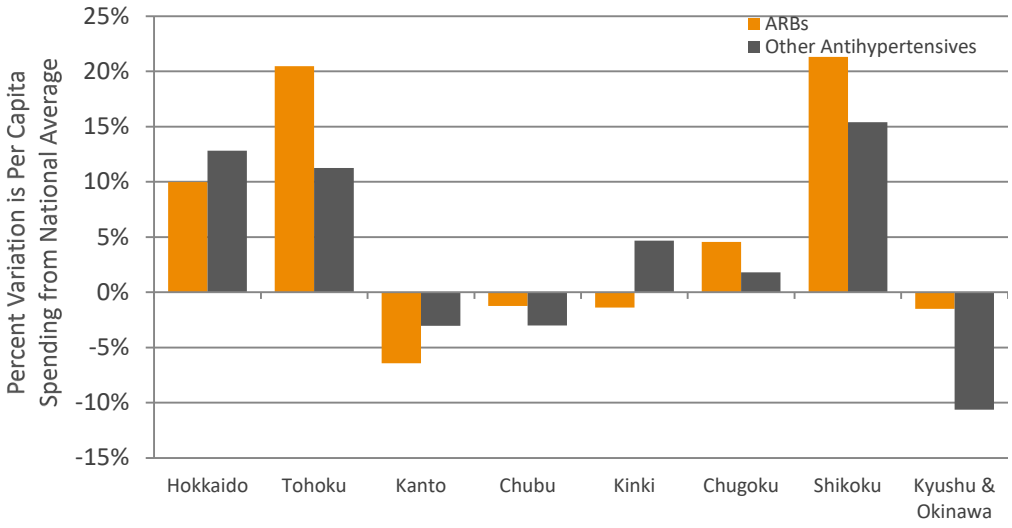


Source: Encise Research Center, Encise Inc.

Variations in ARBs and other anti-hypertensives by Regions:

- **Shikoku** as region has the highest per capita use of anti-hypertensives (ARBs 21%, while other anti-hypertensives 15% higher than the national average per capita use), followed by **Tohoku** (20% higher for ARB and 11% higher for other anti-hypertensives) and **Hokkaido** (10% and 13% respectively)
- **Kyushu & Okinawa** as region has the lowest use of anti-hypertensives compared to national average per capita use (-1% for ARBs and -12% for others) followed by **Kanto** (-6% and -3%) and **Chubu** (-1%, -3% respectively).

Chart 7.
Per Capita Sepnding on ARBs vs. Other Anti-hypertensives by Region



Source: Encise Research Center, Encise Inc.

Conclusion

ERC reiterates that the objective of this study is not to provide any recommendations or directions. The purpose of the study was only to look into a relatively less explored area of variations into drug use practices by geographic regions, and present a landscape of factual ground scenarios for a select class of drugs.

ERC leaves it completely on the readers on how they want to interpret and use the findings. However, the observations from the relative study of per-capita spending of the selected therapeutic classes bring a few interesting points for further examination.

The choice of selection of drugs (in case of therapeutically closely related drugs, or substitutable drugs), or the choice of time of switching of drugs (where drugs are generally switched to different class with the progression of diseases) – varies significantly with the geographic region. This situation suggests two hypotheses -

1.) Some doctors are achieving desired therapeutic outcome with the conventional drugs (or switching late to the more expensive drugs) than the novel drugs (or switching early to more expensive options). The learnings from these therapeutic practices could be utilized into other regions to attain economic benefits.
2.) Some doctors are missing the opportunity to attain desired therapeutic outcome in a better way by not using effective novel medications (or by not switching early to more expensive options). Thereby, they are depriving some patients from availing superior therapeutic options and hence still creating a health-economic burden to the society.

In any case, it would be a win-win situation for the society, health provider communities, and regulators to examine the underlying factors behind the variations in these drug-use practices. A better understanding of this issue may optimize therapeutic practices and also open a new window for economic savings.

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