Monitoring for adverse drug events of high-risk medications with a computerized clinical decision support system: A prospective cohort study

Running title: Monitoring with a CDSS

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Abstract

Background

Monitoring is recommended to prevent severe adverse drug events, but such examinations are often missed. To increase the number of monitoring that should be ordered for high-risk medications, we introduced a clinical decision support system (CDSS) that alerting and ordering the monitoring for high-risk medications in an outpatient setting.

Methods

We conducted a 2-year prospective cohort study at a tertiary care teaching hospital before (phase 1) and after (phase 2) the activation of a CDSS. The CDSS automatically provided alerts for liver function tests for vildagliptin, thyroid function tests for immune checkpoint inhibitors (ICIs) and multikinase inhibitors (MKIs), and a slit-lamp examination of the eyes for oral amiodarone when outpatients were prescribed the medications but not examined for a fixed period. The order of laboratory tests was automatically appeared if alert was accepted. The alerts were hidden and did not appear on the display before activation of the CDSS. The outcomes were the number of prescriptions with alerts and examinations.

Results

During the study period, 330 patients in phase 1 and 307 patients in phase 2 were prescribed vildagliptin, 20 patients in phase 1 and 19 patients in phase 2 were prescribed ICIs or MKIs, and 72 patients in phase 1 and 66 patients in phase 2 were prescribed oral amiodarone. The baseline characteristics were similar between the phases. In patients prescribed vildagliptin, the proportion of alerts decreased significantly (38% vs 27%, P<0.0001), and the proportion of examinations increased significantly (0.9% vs 4.0%, P<0.0001) after activation of the CDSS. In patients prescribed ICIs or MKIs, the proportion of alerts decreased significantly (43% vs 11%, P<0.0001), and the proportion of examinations increased numerically, but not significantly (2.6% vs 7.0%, P=0.13). In patients prescribed

oral amiodarone, the proportion of alerts decreased (86% vs 81%, *P*=0.055), and the proportion of examinations increased (2.2% and 3.0%, *P*=0.47); neither was significant.

Conclusion

The CDSS has potential to increase the monitoring for high-risk medications. Our study also highlighted the limited acceptance rate of monitoring by CDSS. Further studies are needed to explore the generalizability to other medications and the cause of the limited acceptance rates among physicians.

Introduction

Adverse drug events (ADEs) are the most common adverse medical events in the inpatient and outpatient settings with the prevalence of 1.9% to 58%.[1-5] Some ADEs were caused by errors, and most errors related to ADEs occurred at the ordering stage, and 67% of errors at the ordering stage were not intercepted.[6] Therefore, preventing or reducing the errors at ordering stage is one of the effective strategies to prevent ADEs. This is especially relevant in outpatient setting because the medications or symptoms were not well scrutinized once the medications were administered and patients returned their home. In addition, a large number of patients are treated in outpatient settings, and once-missed examinations could be noticed several months later in outpatient settings. To improve the process of medication use in an outpatient setting, automated alert systems to provide recommendations to physicians have the potentials to detect ADEs and reduce errors.[7,8]

A computerized clinical decision support system (CDSS) provides physicians with alerts that indicate the appropriate actions by text messages. Many reports have explored the effectiveness of a CDSS on medication orders, including the avoidance of medications in patients with a history of allergies,[9,10] prescription of appropriate doses for those with decreased renal function or pediatrics,[11-13] adherence to guidelines,[14,15] or recommendations for monitoring.[16,17] Monitoring is recommended for high-risk medications in official drug package inserts to prevent or alleviate severe ADEs. However, such recommendations have often not received much attention in clinical settings, and the examinations are often missed.[18] CDSSs with alert systems improved clinical process, but the effects were limited and depend on the systems or medications.[8] To investigate what kind of medications to which a CDSS is more effective in outpatient settings, we conducted a prospective cohort study. We added direct ordering function to alerting function on CDSS to improve the acceptance among physicians in this study because previous studies evaluated

the CDSS for monitoring with alerting function only.[16,17]

Methods

Study design and patients

We conducted a prospective cohort study at outpatient service of XXX hospital, a tertiary care teaching hospital with 618 beds with 28 departments in Japan. The hospital is equipped with the Integrated Intelligent Management System (IIMS), consisting of electronic medical record (EMR), computerized ordering system, nursing logs, laboratory and imaging results, prescription data, and hospital claims.[12,14] This system was locally developed at XXX hospital in conjunction with Fujitsu. The study was conducted from 1 October 2017 to 30 September 2019, and the computerized CDSS for recommending examinations based on the official drug package inserts of the target medications was activated on 1 October 2018. We selected vildagliptin, immune checkpoint inhibitors (ICIs), multikinase inhibitors (MKIs) and oral amiodarone as the target medications because their official drug package inserts instructed examinations during their use to prevent severe side effects.[19-27] The study period was divided into 1 year before activation of the computerized CDSS (phase 1: October 2017 to September 2018) and 1 year after its activation (phase 2: October 2018 to September 2019). We included all outpatients who had prescriptions of any of these target medications at any point during the study period.

The index date was the day of prescription of the target medication to the patient. Patients might have multiple index dates if they were prescribed them at outpatient clinics more than once during the study period. When the index date was before 1 October 2018, such patients were included in phase 1, and patients whose index date was 1 October 2018 or later were included in phase 2. Although some patients were followed beyond 1 October 2018, and each index date of target medications was included in both phase 1 and phase 2, each patient was included in either phase 1 or phase 2 according to the earliest index date.

Target medications

We searched the official drug package inserts of medications in the list of high-risk medications at the study hospital and assessed the degree of recommendation of monitoring. Discussion among investigators and hospital pharmacists reached the conclusions that vildagliptin, immune checkpoint inhibitors (ICIs), multikinase inhibitors (MKIs) and oral amiodarone were selected as the target medications considering the degree of recommendation of monitoring based on the official drug package inserts, the low adherence of monitoring, and the increase in prescription at the study hospital. These medications were strongly recommended to monitor the liver function (vildagliptin), thyroid function (ICIs and MKIs), and slit-lamp examination of the eyes (oral amiodarone) in the official drug package insert during their use to prevent severe side effects. ICIs included nivolumab, pembrolizumab, and atezolizumab, and MKIs included pazopanib, regorafenib, axitinib, and sunitinib at the time of the study.

To investigate the differences in behavior of physicians between recommended examinations, three cohorts were constructed according to the target medications (vildagliptin, ICI or MKI, and amiodarone). If a patient was prescribed more than one target medication during the study period, that patient was included into more than one cohort independently.

Development and Implementation of the CDSS

We developed the CDSS alerting and ordering the monitoring for the target medications (Supplementary Figure S1). When a physician ordered the target medication, the CDSS obtained the information about the target medication and monitoring that were conducted for certain periods in the past, and it assessed whether the examination should be recommended. If there is no monitoring data during a specific time period when a

physician ordered the target medication, an alert is generated in the EMR. Physicians could decide whether to accept the recommended examinations. To reduce the burden of physicians, we did not collect the reasons when they did not accept the alert.

When a physician ordered vildagliptin, the CDSS obtained information on blood tests of liver function (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and γ-glutamyl transpeptidase) for the previous 3 months. If any of these four items were not examined in the previous 3 months, an alert recommending these four blood tests appeared on the display in the EMR when a physician tried to confirm a vildagliptin prescription.

When a physician ordered any ICI or MKI, the CDSS obtained information on blood tests of thyroid function (thyroid stimulating hormone, free triiodothyronine, and free thyroxin) for the previous 3 months. If any of these three items were not examined, an alert recommending these three blood tests appeared.

When a physician ordered oral amiodarone, the CDSS obtained information on slit-lamp examination of the eyes for the previous one year. If the patient did not have an examination, an alert recommending the examination appeared.

The developed CDSS utilized interruptive alerts and direct transfer to order liver function test and thyroid function test. The laboratory test order screen automatically appeared on the display (Figure 1), if a physician accepted the recommendations from the alerts by clicking the examination button. The slit-lamp examination screen did not appear automatically, and the physician had to open the order screen for referral to ophthalmology himself. Physicians could reject the alert for recommended examinations if they considered them unnecessary.

We implemented the CDSS on the IIMS on 1 October 2017, but the CDSS worked in the background until 30 September 2018 (phase 1), and alerts did not appear on the screen on the IIMS. All logs of patients' and prescriptions' data target medications and

potential alert opportunities were stored during this period. The CDSS was activated on 1 October 2018 and continued to 30 September 2019 (phase 2). Therefore, physicians could not use the CDSS until 30 September 2018. After 1 October 2018, the CDSS alerts were displayed on the IIMS, and physicians were guided by the CDSS and could see the alerts and decide whether to accept the recommended examinations. All physicians were notified about the CDSS but there were no other activities regarding the CDSS alerting and ordering the monitoring for high-risk medications.

Data collection

We collected patients' characteristics on the earliest index date during phase 1 and phase 2 separately. All data on target medications, examinations and outpatient visit history were collected from the IIMS, as well as data on all hidden and displayed alerts and responses by physicians to the alerts. The data consisted of patient-level and prescription-level data. Patient-level data included age, sex, history of smoking, laboratory data, diseases, and specialty of the physician in charge. Prescription-level data included the kinds and doses of each target medication, orders for recommended examinations, and alerts for such examinations by each target medication.

Outcomes

The outcomes were the number of alerts and the actual orders for recommended examinations at prescription-level. The acceptance rates of alerts were calculated by the number of prescriptions with examinations divided by the number of prescriptions with alerts for examinations for each target medication. The alerts were hidden in the background and did not appear on the display in phase 1; thus, orders for each examination in phase 1 were considered voluntary.

Statistical Analyses

We presented the patient-level data as median and interquartile range (IQR) for continuous variables, and as numbers and percentages for categorical variables stratified by phase 1 and phase 2 in each cohort of target medications. Patients' background characteristics were compared between phase 1 and phase 2 in each cohort using the *t*-test or the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables.

In the prescription-level data, the proportions of prescriptions with alerts or examinations per all prescriptions of target medications were compared between phase 1 and phase 2 in each cohort using chi-squared tests. Because patients' background characteristics were considered similar between phase 1 and phase 2, adjusted analyses were not performed. We conducted interruptive time series analyses to evaluate the differences in temporal trend of proportion of alerted prescriptions per month between phases.

All statistical analyses were performed using JMP 15 (SAS Institute, Cary, NC). *P* values were two-tailed, and *P* values less than 0.05 were considered statistically significant.

Results

Included patients

There were 74 757 outpatients (37 661 in phase 1 and 37 096 in phase 2) during the study period. Of them, 637 patients were prescribed vildagliptin, 39 patients were prescribed ICIs or MKIs, and 138 patients were prescribed oral amiodarone (Figure 2).

Vildagliptin cohort

Patient characteristics were similar between phase 1 and phase 2 (Supplementary Table S1).

Of the 330 patients in phase 1 when alerts were not displayed on the screen, 155 patients (47%) had at least one vildagliptin prescription that needed alerts for liver function blood tests and 15 patients (4.5%) underwent liver function tests without alert. In phase 2 when alerts were displayed on the screen, 143 of 307 patients (47%) had at least one vildagliptin prescription that needed alerts for liver function blood tests, and 58 patients (19%) underwent liver function tests (Table 1). The median number of alerts for an alerted patient was 4 in phase 1 (hidden alert) and 3 in phase 2 (Supplementary Table S4). The proportion of prescriptions with alerts for liver function blood tests decreased significantly (38% in phase 1 and 27% in phase 2, $P < 0.0001$), and the proportion of prescriptions with conducted blood tests increased significantly (0.9% in phase 1 and 4.0% in phase 2, $P < 0.0001$) (Table 1). The proportion of vildagliptin prescriptions subject to alerts decreased gradually after activating the CDSS (Figure 3A).

ICI or MKI cohort

All patients had malignant neoplasms, and 90% of them were located in either digestive organs or the urinary tract (Supplementary Table S2).

The proportion of patients with alerts decreased (55% in phase 1 and 47% in phase 2) and the proportion of patients with examinations increased (15% in phase 1 and 32% in phase 2) (Table 1). The median number of alerts for an alerted patient was 4 in phase 1 (hidden alert) and 1 in phase 2 (Supplementary Table S4). For prescription-level data, the proportion of alerts decreased significantly (43% in phase 1 and 11% in phase 2, $P < 0.0001$) (Table 1 and Figure 3B). The proportion of examinations increased numerically (2.6% in phase 1 and 7.0% in phase 2), but there was no significant difference (Table 1).

Amiodarone cohort

All patients had arrhythmias and a history of chronic heart failure (Supplementary Table S3).

The proportion of patients with alerts increased (89% in phase 1 and 94% in phase 2) and the proportion of patients with examinations increased (5.6% in phase 1 and 12% in phase 2) (Table 1). The median number of alerts for an alerted patient was 6 in phase 1 (hidden alert) and 5 in phase 2 (Supplementary Table S4). For prescription-level data, although the percentage of monthly prescriptions with alerts was still high in phase 2 (Figure 3C), the proportion of alerts decreased (86% in phase 1 and 81% in phase 2, $P = 0.055$) (Table 1) but there was no significant difference. Proportion of examinations increased numerically (2.2% in phase 1 and 3.0% in phase 2), but there was no significant difference.

Acceptance rates in phase 2

In phase 2 when CDSS alerts were displayed on the IIMS, 15% (67/452) of alerts for vildagliptin were accepted by physician. Those for ICIs or MKIs and amiodarone were 62% (8/13) and 3.7% (12/324), respectively.

Discussion

Statement of principal findings

We developed the CDSS that alerting and ordering the monitoring which was recommended in the official drug package inserts for vildagliptin, ICIs, MKIs, and oral amiodarone. After activating the CDSS, the proportion of prescriptions with necessitating the alerts were decreased and the proportions of monitoring were increased numerically for all target medications, but the acceptance rates of alerts for monitoring were limited.

Interpretation within the context of the wider literature

CDSSs with alert systems were reported to improved clinical process at the prescription-level, but not necessarily improve the clinical outcomes at the patient-level.[8] Kwan et al. reported that CDSSs produced an average absolute improvement of 5.8% in the percentage of patients receiving desired care.[28] The reasons for small improvement with CDSS were due to the alerts itself which were not consistent with clinical objectives and alert fatigue. Alert fatigue was caused by the alert that was not serious, irrelevant, or shown repeatedly. These alerts became less important and interfered with the practice of physicians, leading to overriding alerts. Thus, recommended actions implemented in the CDSS should be in line with current clinical practice and acceptable by target physicians. Our CDSS was effective for improving test order rates only in some groups of patients, but the absolute acceptance was low. We developed the alert systems if at least one of tests were not examined in this study to ensure that physicians could avoid the risk for patients as much as possible. However, not all liver function tests or thyroid function tests were need to be performed clinically. Future research needs to develop CDSSs which meet clinical objectives in more detail.

There were no significant increases in the proportion of examinations in the ICI or

MKI cohort and the amiodarone cohort. Compared to the severity of diseases for which ICIs, MKIs and oral amiodarone are prescribed, the conditions that alerts tried to prevent were less severe, such as thyroid dysfunction and ophthalmic disorders. Slight et al. showed that drug allergy alerts for non-life-threatening symptoms are more likely to be overridden than alerts for life-threatening symptoms.[29] If physicians felt the alert was more minor than the target disease, the acceptance rate of alerts may have been lower. Indeed, the reason why the acceptance rate of alerts was low after activating the CDSS in the amiodarone cohort might be due to the fact that ophthalmic examinations necessitated the consultations to other physicians. Thus, the type of action required was also explored as determinant of acceptance of alerts, and consultation to other physicians could be one of the difficult targets for a CDSS in current clinical practice.[30]

Implications for policy, practice and research

The CDSS was generally effective for providing alternative actions to physicians, but some CDSSs may not be effective for physicians who were confident in their judgement. A recent study implied that the acceptance rate of alerts based on a clinical practice guideline for glucocorticoid-induced osteoporosis was higher for physicians in general internal medicine than in other subspecialties.[14] This study and the present findings supported that a CDSS for medications primarily prescribed by specialists only could not be effective. High-risk medications that were frequently prescribed by many physicians irrelevant of the specialty could be effective target medications.

Strengths and limitations

We implemented a CDSS with an interruptive alert system with short-cut ordering of laboratory tests. Our study had several limitations. First, this was an observational study

comparing practices before and after the activation of a CDSS. Second, we did not collect the identification information of physicians nor the reasons why physicians did not accept the alerts. Therefore, we could not analyze the differences between physicians or kinds of tests. These data should be collected and investigated to improve the acceptance rate. Third, we were able to determine the number of examinations, but unable to evaluate the results of examinations or the presence of ADEs. In addition, we did not collect the data of whether the physicians who ordered the monitoring checked the results. Therefore, it was unclear whether true ADEs could be reduced with the CDSS. Fourth, we included all outpatients in a tertiary care hospital for 2 years, but the sample size was not large enough to explore the changes in the monitoring and alerts generated by the CDSS. Therefore, the results of patient-level data should be interpreted carefully. The proportions of patients with alerts were numerically stable for vildagliptin, decreased for ICIs or MKIs, and increased for amiodarone. Generally, if a patient had an alert for the target medication and physician accepted the alert, the number of alerts at prescription-level decreased because the next prescription did not have the alert. If patients were followed with short intervals, the proportion of alert per patient in phase 2 decreased because they were alerted in phase 1. This should be the case of ICIs or MKIs because patients with such medications were those with active malignant diseases. On the contrary, patients on vildagliptin or amiodarone were those with chronic diseases, such as diabetes or arrhythmia. Because they were followed by the other facilities and occasionally referred to the study hospital for consultation, the proportions of alert per patient in phase 2 were stable for or even increased by chance. Therefore, prescription-level data should be primarily interpreted in this study. Finally, this study was conducted in a single center, which limited its generalizability. Although the intervention was simple, and the results seemed applicable to other settings, further studies should be conducted to confirm our findings.

Conclusion

We developed and evaluated the CDSS alerting and ordering the monitoring for high-risk medications in an outpatient setting. After the activation of the CDSS, the monitoring for some of high-risk medications were increased. However, the acceptance rates of alerts for monitoring were limited.

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Table 1. Results of alerts and examinations in each medication cohort

	Patients, n (%)		Prescriptions, n (%)			
	Alert	Exam	Alert	*P* value	Exam	*P* value
Vildagliptin						
Phase 1 (330 patients with 1701 prescriptions)	155 (47)	15 (4.5)	643 (38)	<0.001	15 (0.9)	<0.001
Phase 2 (307 patients with 1668 prescriptions)	143 (47)	58 (19)	452 (27)		67 (4.0)	
Immune checkpoint inhibitors or multikinase inhibitors						
Phase 1 (20 patients with 114 prescriptions)	11 (55)	3 (15)	49 (43)	<0.001	3 (2.6)	0.13
Phase 2 (19 patients with 115 prescriptions)	9 (47)	6 (32)	13 (11)		8 (7.0)	
Amiodarone						
Phase 1 (72 patients with 451 prescriptions)	64 (89)	4 (5.6)	389 (86)	0.055	10 (2.2)	0.47
Phase 2 (66 patients with 398 prescriptions)	62 (94)	8 (12)	324 (81)		12 (3.0)	

Figure legends

Figure 1. Screenshots of alerts and orders

Clicking the confirm button (circled) in the alert screen on the left will display the order screen on the right.

Figure 2. Study flowchart

Figure 3. The number of all prescriptions and the percentage of alerted prescriptions

A. Vildagliptin

Bars represent the number of prescriptions. Square dots and round dots represent the percentages of prescriptions which were alerted in phase 1 and phase 2, respectively. Straight lines indicate regression lines for alert percentages in each phase. The slopes of the regression lines were 0.28 and -1.08 for phase 1 and phase 2, respectively (P = 0.0026).

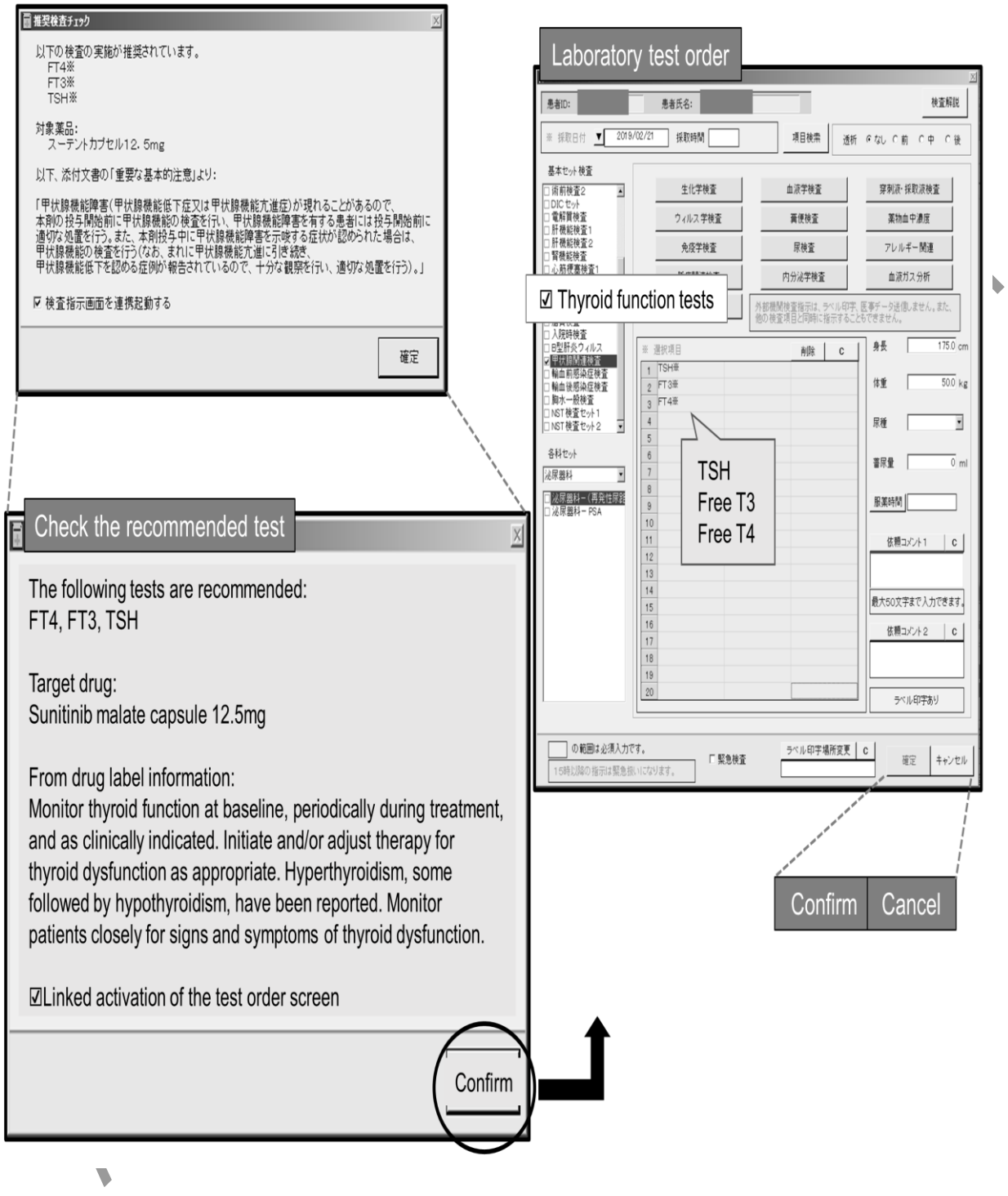
B. Immune checkpoint inhibitors or multikinase inhibitors

Bars represent the number of prescriptions. Square dots and round dots represent the percentages of prescriptions which were alerted in phase 1 and phase 2, respectively. Straight lines indicate regression lines for alert percentages in each phase. The slopes of the regression lines were -0.86 and 1.38 for phase 1 and phase 2, respectively (P = 0.15).

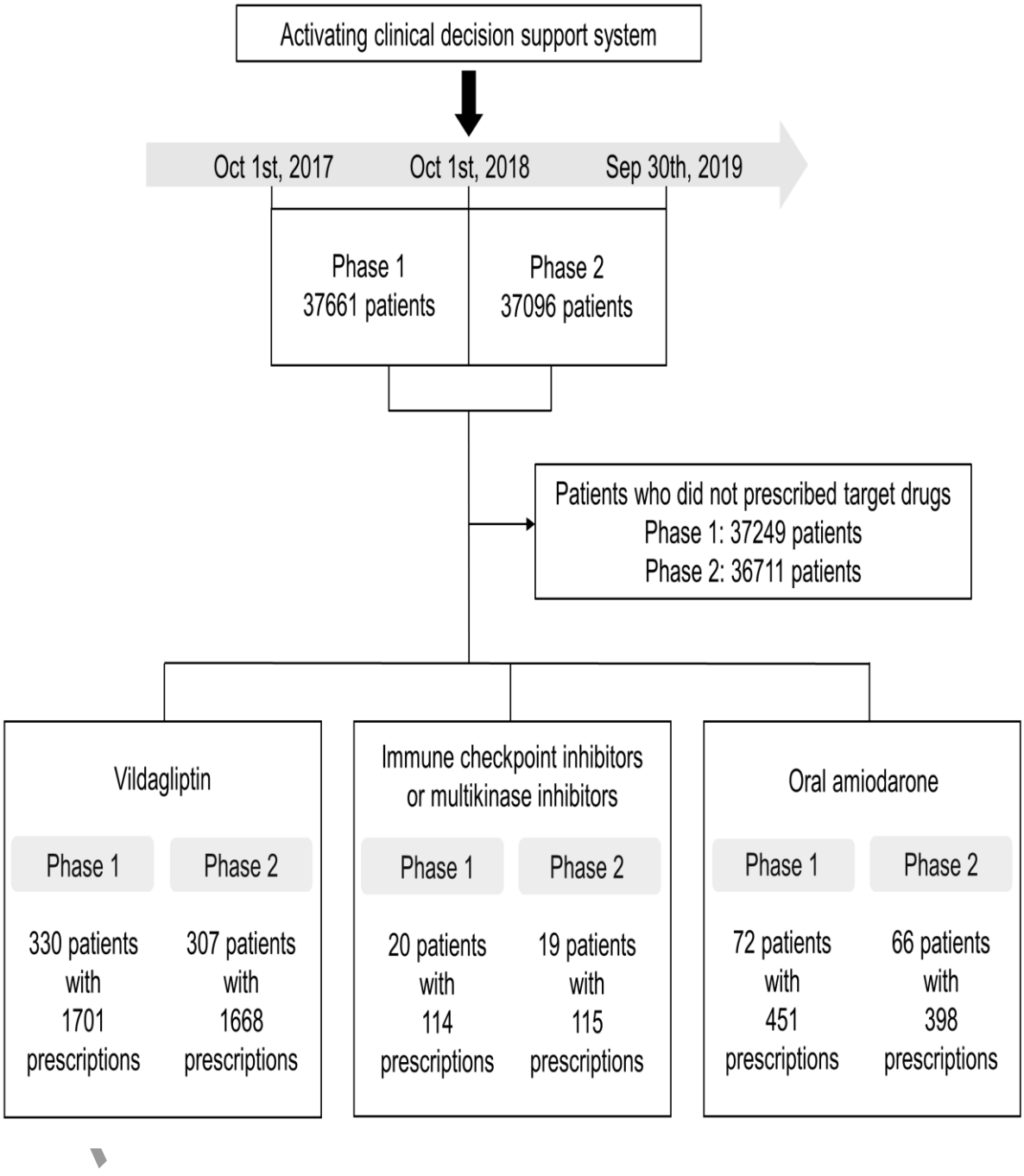
C. Oral amiodarone

Bars represent the number of prescriptions. Square dots and round dots represent the percentages of prescriptions which were alerted in phase 1 and phase 2, respectively. Straight lines indicate regression lines for alert percentages in each phase. The slopes of the regression lines were -1.13 and 1.03 for phase 1 and phase 2, respectively (P = 0.0002).

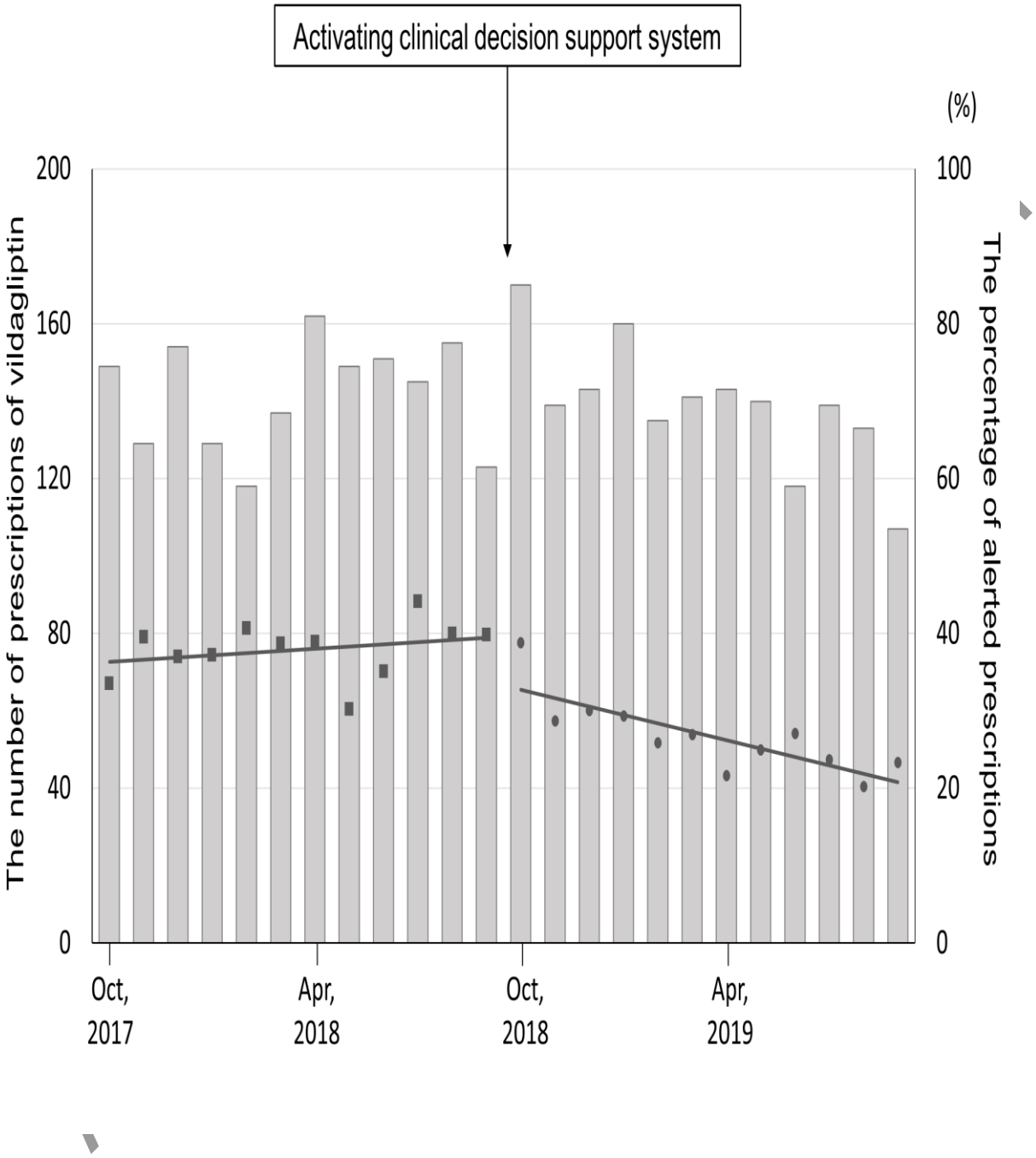
[[Figure 1]]



[[Figure 2]]



[[Figure 3A]]



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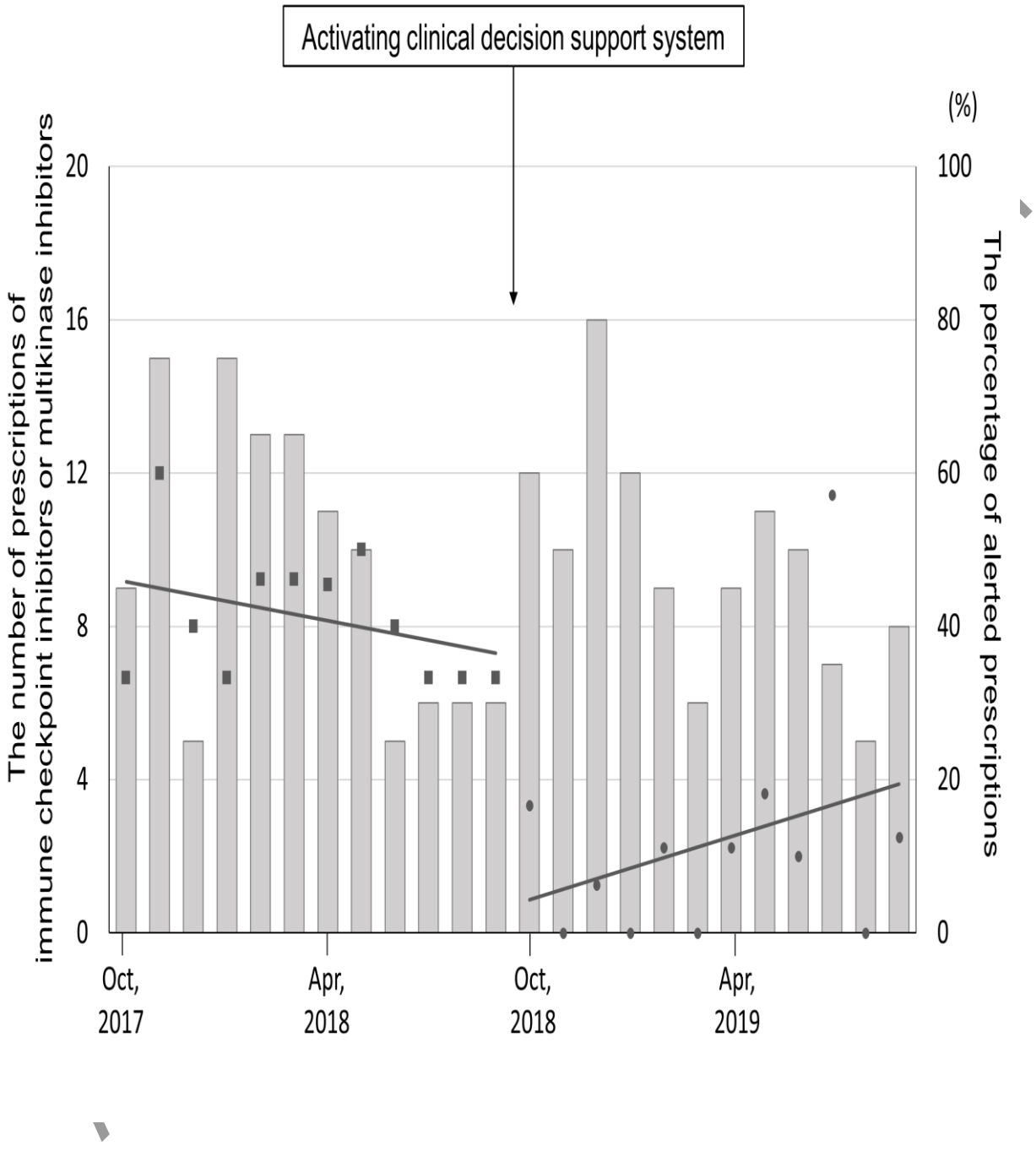

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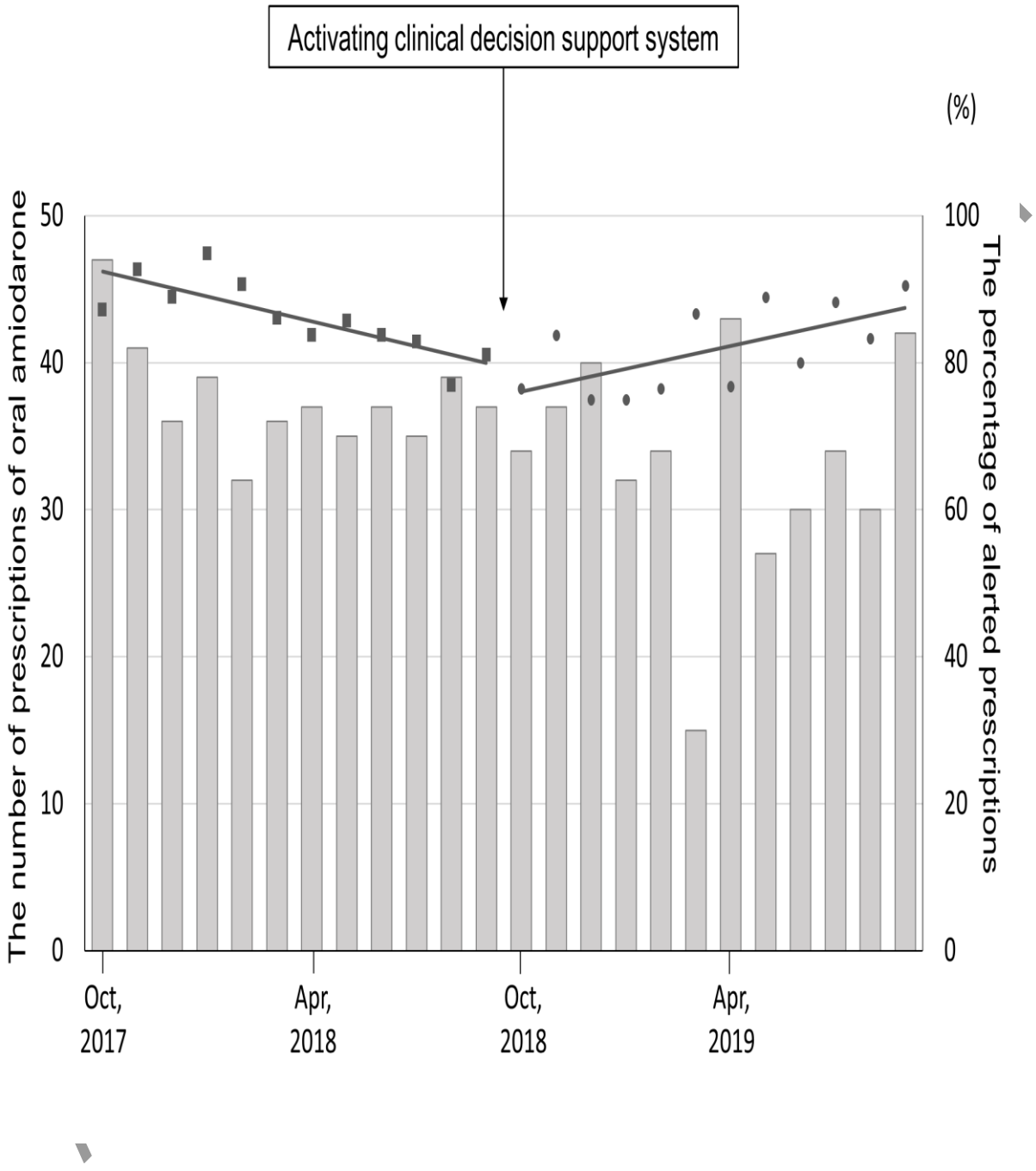

Contributorship

M.N. performed the statistical analyses, interpreted the results, and drafted the manuscript; M.S. designed the study, acquired the data, managed the data, performed the statistical analyses, interpreted the results, and drafted the manuscript; T.N. designed the study, acquired the data, interpreted the results, and critically reviewed the manuscript; T.S. designed the study, interpreted the results, and critically reviewed the manuscript; C.M. designed the study, interpreted the results, and critically reviewed the manuscript; J.T. interpreted the results and critically reviewed the manuscript; Y.O. designed the study, interpreted the results, and critically reviewed the manuscript; S.K. acquired the data, interpreted the results, and critically reviewed the manuscript; and T.M. conceptualized the study, designed the study, obtained the funding, acquired the data, interpreted the results, drafted the manuscript, and supervised the whole study process. All authors read and approved the final manuscript.

Ethics and other permissions

This study was approved by the Institutional Review Boards of Hyogo Medical University and Shimane Prefectural Central Hospital. We used an opt-out method to replace written, informed consent from each patient according to the approvals of these review boards. All study methods were carried out based on the Japanese Ethical guidelines for Medical and Health Research involving Human Subjects and the Declaration of Helsinki.

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Conflicts of interests

All authors have declared that they do not have any conflicts of interest pertaining to this manuscript.

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Data availability statement

The data will be shared on reasonable request to the corresponding author.