



Identifying Trends in Co-prescription of Tamoxifen with CYP2D6 Inhibitors

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Introduction

- Tamoxifen, a selective estrogen receptor modulator (SERM), is a medication utilized mainly in the management and prevention of breast cancer and is prescribed for a various labeled and off labeled indications.
- Tamoxifen needs to be metabolized in the body by certain enzymes, CYP2D6, to yield more potent metabolite.
- Endoxifen, the 100 time more potent metabolite than tamoxifen primarily exerts the anti-tumor activity and is mainly produced by CYP2D6 enzyme.
- Endoxifen needs to establish certain plasma concentration in the body in order to be effective.
- Tamoxifen has notable side effects including hot flashes and night sweats.
- Certain medications are prescribed to alleviate these tamoxifen related side effects such as selective serotonin reuptake inhibitors (SSRIs), especially for long periods given that tamoxifen is typically prescribed for 5 years.
- The problem of SSRIs among other drugs is that they can inhibit action of CYP2D6 enzyme and prevent metabolism of tamoxifen and ultimately its action.
- More and more patients reports poor adherence to tamoxifen which might be attributed to drug related side effects
- The prevalence of co-prescription of tamoxifen and these CYP2D6 inhibitors is unknown in Saudi Arabia.

Aim and objectives

Aim:

Our aim was to observe how often did patients received concomitant adjuvant hormonal therapy, specifically tamoxifen with CYP2D6 inhibitors.

Objectives:

- Identify number of patients who received tamoxifen during June 2015 – June 2017.
- Identify supply coverage to tamoxifen during this period.
- Identify prevalence of co-prescription of tamoxifen with CYP2D6 inhibitors during the study period.

Method

This was a descriptive retrospective cross-sectional study. We looked into pharmacy data of two major hospitals in Riyadh, Saudi Arabia. Data from King Saud University Medical City (KSUMC), a tertiary care and referral hospital with more than 1000 bed capacity, and Prince Sultan Military Medical City (PSMMC) were reviewed. All patients who had at least one tamoxifen prescription in their electronic medical records (EMRs) from June 2015 to June 2017 were included. Patients who had other adjuvant hormonal therapy e.g. letrozole were excluded from the study. Retrieved data included demographic characteristics such as sex and age. We then went through the American Food and Drug Authority (FDA) website as a reference for categorizing CYP2D6 inhibitors into the following categories (according to *examples of clinical inhibitors for P450-mediated metabolisms* table): strong (bupropion, fluoxetine, paroxiten, quinidine, and terbinafine) moderate (cimetidine, cinacalcet, duloxetine, fluvoxamine, and mirabegron), and weak (abiraterone, amiodarone, celecoxib, cimetidine, clobazam, cobicistat, desvenlafaxine, escitalopram, labetalol, lorcazerin, ritonavir, sertraline, and vemurafenib). After that we did a matching of those drugs with EMRs of patients on tamoxifen to find which CYP2D6 inhibitor was prescribed concomitantly with tamoxifen during the study period. To assess supply coverage of tamoxifen in one year we included all patients who received tamoxifen at least twice and had 12 or more months separating those two entries. This ensured that all included patients received tamoxifen for at least one year. Next, we counted 12 months starting from the first entry and labeled this year Measured Year (MY). Since tamoxifen is taken daily the number of days of supply in the system will indicate the fraction of a year when patient had coverage for tamoxifen. We used the following equation to calculate supply coverage:

$$\text{Supply Coverage (\%)} = \frac{\text{Days of supply in MY}}{365} \times 100$$

Additionally, we performed a subgroup analysis of KSUMC patients EMRs, in attempt to find any labeled and off label indications for tamoxifen prescriptions.

Results

During the study period, 435 patients received tamoxifen from pharmacy. Of those 20 were male (4.5%). The average age of males was 50 years. Two hundred and sixteen female out of the 415 (52.1%) were ≥ 45 years old and their average age was 53 years. The other 199 (47.9%) had an average age of 36.6 years. In the first year 158 patients received tamoxifen. In the second year of the study 206 received tamoxifen with 174 patients persisting from the previous year (Figure 1). One hundred and seventy one patients used tamoxifen for duration of ≥ 12 months (39.3%). Thirty percent of these patients had a supply coverage of $< 85\%$ (Figure 2). The identified strong CYP2D6 inhibitors that was co-prescribed with tamoxifen included only Bupropion. No moderate inhibitors were identified during the study period. The co-prescribed weak inhibitors included: escitalopram, sertraline, celecoxib, and venlafaxine. Figure 3 and Figure 4 shows the prevalence of co-prescription of tamoxifen with CYP2D6 inhibitors in the first and second year of the study period, respectively. Generally, the prescription of strong inhibitors with tamoxifen decreased in the second year with increase in the prescription of weak inhibitors. A subgroup analysis of KSUMC patients revealed that Two of the males were diagnosed of breast cancer and one didn't have any indications for tamoxifen therapy (n=3). The majority of females in KSUMC had diagnosis of breast cancer (n= 131, 98.5%) regardless of the stage. One female had ovarian cancer (0.75%) and one didn't have any indications for tamoxifen treatment (0.75%).

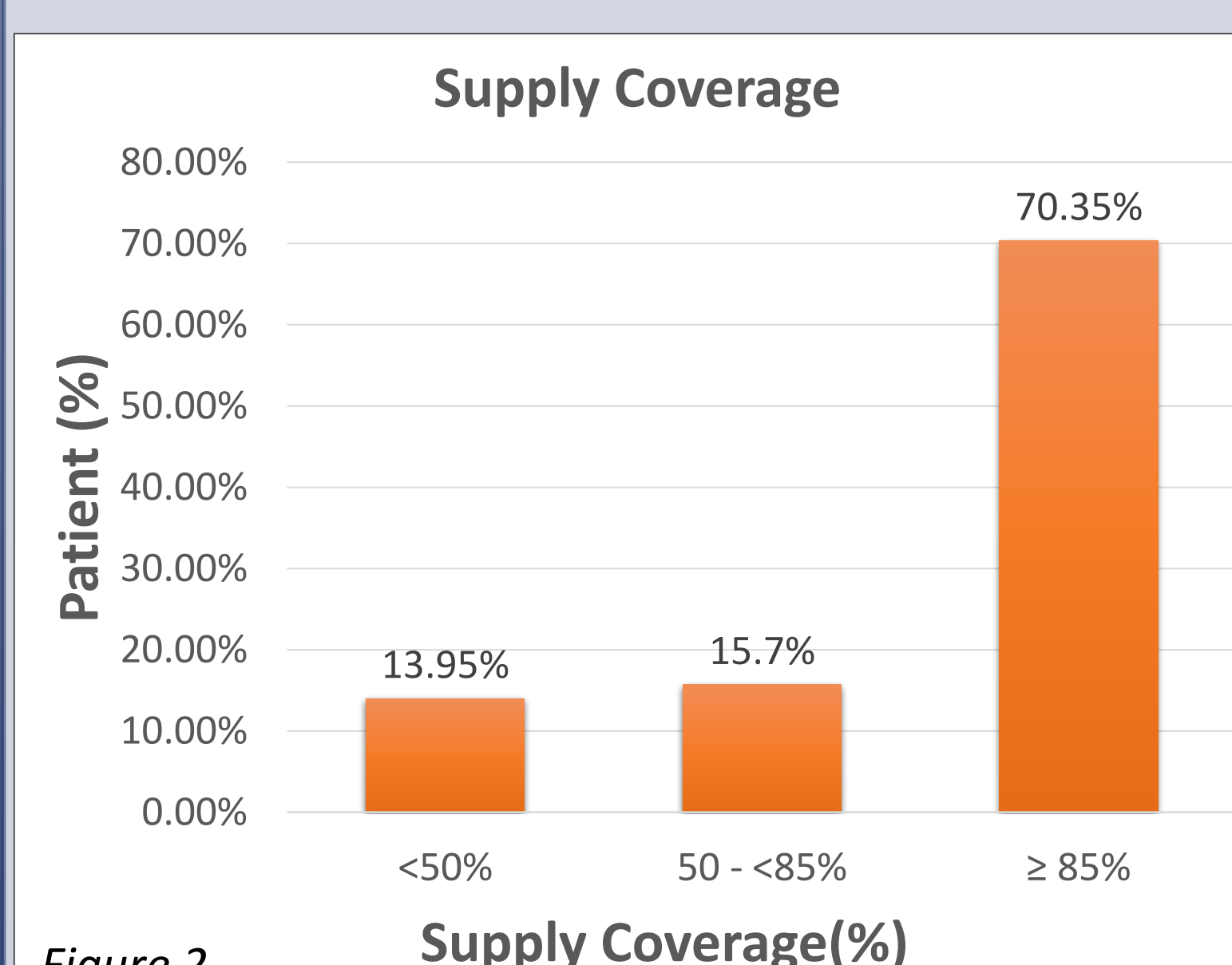
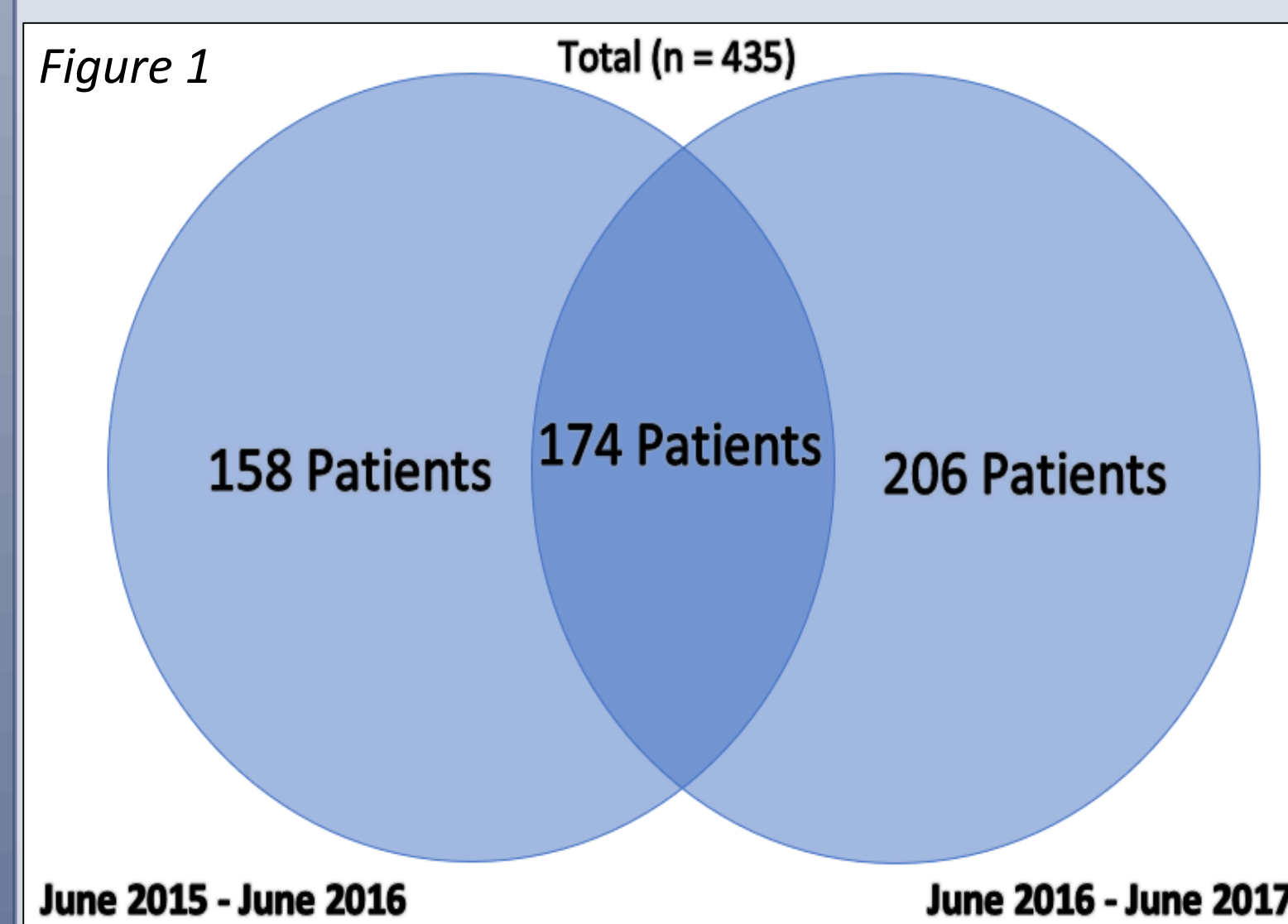
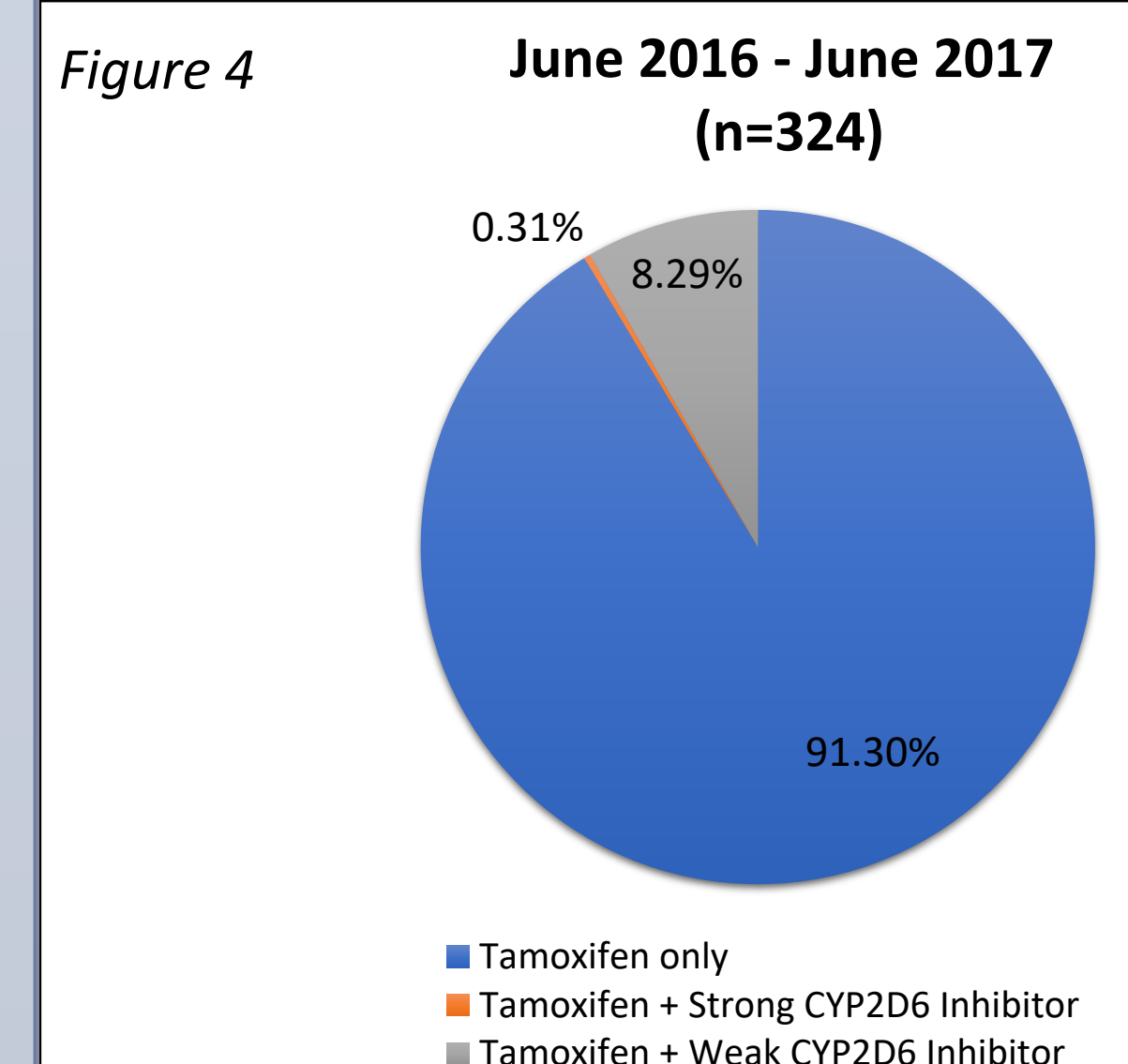
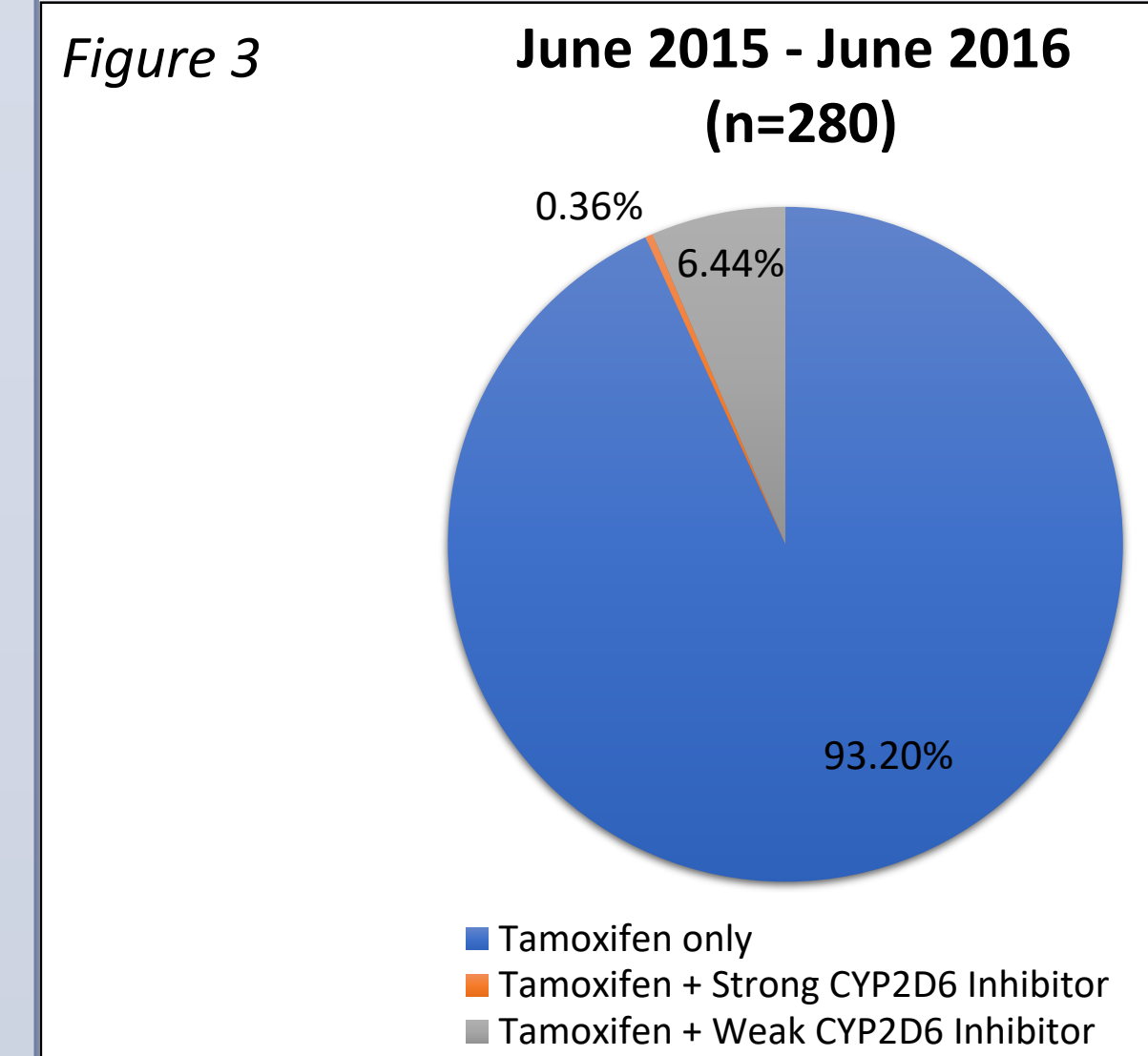


Figure 2



Conclusion

During a two-year period the number of patients received tamoxifen increased inside two major hospital in Riyadh, Saudi Arabia. The majority of these were female of 45 year old or older. When tamoxifen is used for ≥ 1 year about third of the patients seemed not to get enough supply. Further research is needed to identify why those patients had low supply during one year period. There is minimal co-prescription of strong CYP2D6 inhibitors with tamoxifen. There is a need to investigate the long term effect of co-prescription of these CYP2D6 inhibitors given that some patients might be poor metabolizer with regard to CYP2D6 enzyme which might put them at risk of decreased plasma level of endoxifen and subsequently breast cancer recurrence. Additionally, knowing genetic polymorphism of this particular drug metabolizing enzyme in Saudi Arabia might help in identifying the percentage of poor metabolizers who concomitantly take tamoxifen with CYP2D6 inhibitors which are at greater risk of recurring breast cancer comparing to normal metabolizers.

References



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