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Cardiovascular Safety of Febuxostat and Allopurinol in Gout/ Hyperuricemia Patients: A Retrospective Cohort Event Reporting in A Tertiary Healthcare Facility

Sonal M. Sekhar Dr

CARDIOVASCULAR SAFETY OF FEBUXOSTAT AND ALLOPURINOL IN GOUT/HYPERURICEMIA PATIENTS: A RETROSPECTIVE COHORT EVENT REPORTING IN A TERTIARY HEALTHCARE FACILITY

A Project Report Submitted to

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(Pharm D)

MANIPAL

ACADEMY *of* HIGHER EDUCATION

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I recommend this piece of work for acceptance for the partial fulfilment of the completion of the 5th year Pharm D program of the Manipal Academy of Higher Education, Manipal for the Academic year 2017-2018.

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Declaration

We hereby declare that the project entitled, **"Cardiovascular Safety of Febuxostat and Allopurinol in Gout/Hyperuricemia Patients: A Retrospective Cohort Event Reporting in a Tertiary Healthcare Facility"** was carried out under the guidance of **Dr. Sonal Sekhar M,** Associate Professor (Selection grade), Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal. The extent and source of information derived from the existing literature have been indicated throughout the project work at appropriate places. The work is original and has not been submitted in part or full for any diploma or degree purpose for this or any other university.

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Acknowledgement

"In the name of God, the Almighty, the most Generous and Merciful"

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Lastly, I offer my regards and blessings to all of those who supported us in any respect during completion of the project

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LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ATP	Adenosine triphosphate
CI	Confidence Interval
CV	Cardiovascular
FDA	Food and Drugs Administration
GIT	Gastrointestinal tract
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
ICD	International Classification of Diseases
KH	Kasturba Hospital
MRD	Medical Records Department
NNH	Number needed to harm
SPSS	Statistical Package for Social Sciences
USFDA	United States Food and Drug Administration

ABSTRACT

Abstract

Background: The Food and Drug Administration (FDA) issued a safety alert in 2017 regarding increased risk of cardiovascular death with febuxostat compared to allopurinol. The drug label of febuxostat already carried a warning sign for cardiovascular adverse events since it was approved in 2009. An additional post-marketing safety trial showed that for all the combined cardiovascular outcomes, febuxostat did not increase the risk compared to allopurinol but it showed an increased risk of cardiovascular mortality. On February 21st, 2019, FDA added a black boxed warning for increased risk of death with febuxostat compared to allopurinol.

Objective: To compare the incidence of cardiovascular events of febuxostat and allopurinol in patients with gout/hyperuricemia and to investigate comparative efficacy of febuxostat and allopurinol on lowering the uric acid levels

Methodology: A hospital-based retrospective cohort study was conducted for a one-year period in hyperuricemia/gout patients admitted from 2013 to 2017. Study cohort (febuxostat/allopurinol/both) and control cohort (drugs other than febuxostat/allopurinol) were selected based on inclusion and exclusion criteria. These patients were retrospectively followed until 31st December 2018. The primary outcomes were cardiovascular events such as cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, urgent revascularization of unstable angina, hospitalization due to heart failure, venous thromboembolism, arrhythmia, transient ischemic attack, urgent cerebrovascular revascularization, death from any cause. IBM SPSS version 20 was used to perform statistical analysis and $p<0.05$ was considered as statistically significant for all the analysis.

Results: The mean difference in the serum urate level for febuxostat was 2.754 mg/dl [p=0.000; CI (95%) 2.209-3.299] and for allopurinol was 1.137 mg/dl [p=0.000; CI (95%) 0.792-1.482]. This indicated both the drugs have the ability in reducing the serum urate levels. However, no significant difference was found between them. The mean survival time for febuxostat was found to be 37 months [CI (95%) 24-51], for allopurinol 107 months [CI (95%) 52-162] and for the group with both drugs it was 38 months [CI (95%) 20-56]. The mean survival time was lesser in febuxostat group than in allopurinol group. However, there was no significant difference between the two groups (p=0.762). Cardiovascular events occurred in 4 out of 71 patients (5.63%) in febuxostat group, 6 out of 93 patients (6.45%) in allopurinol group and 3 out of 10 patients (30%) in group with both drugs. The number needed to harm (NNH) for febuxostat, allopurinol and combination were 22, 19 and 3 respectively in our study. This indicates that there is one cardiovascular event for every 22 patients who are exposed to febuxostat, 19 patients who are exposed to allopurinol and 3 patients who are exposed to both.

Conclusion: Our study shows that both febuxostat and allopurinol are significantly efficacious in reducing serum urate levels. The mean survival time was less for febuxostat compared to allopurinol, which means that cardiovascular events occurred faster in febuxostat group. Incidence of cardiovascular events was more in allopurinol group than in febuxostat group. However, there was no significant difference in these results due to less sample size. Similar to the FDA report, our study also reported that cardiovascular events might occur with chronic usage of febuxostat, allopurinol or both. Therefore, these drugs must be prescribed with caution and should be monitored in patients who already have risk factors for developing cardiovascular diseases.

INTRODUCTION

Introduction

Hyperuricemia is a condition where the uric acid level in the blood is high [1]. The normal uric acid level in our blood is 2.4-6.0 mg/dl for female and 3.4-7.0 mg/dl for male [2]. The body normalizes uric acid levels by keeping a balance between purine input (through diet), amount of uric acid generated (via turn-over of a cell) and the amount which is eliminated in urine or through GIT [3]. At the same time, gout is a type of inflammatory arthritis where there are repeated attacks of a tender, hot, red and swollen joint [4]. The main reason for gout is persistent high levels of uric acid. Crystals of uric acid deposit itself in joints, tendons and other near-by tissues which causes a "Gout attack" [5].

The general occurrence of gout among the population is 1 - 4%. It occurs in 3 - 6% of men and 1 -2% of women. Annual incidence is 2.68 per 1000 persons. Men are 2-6 times more prone than women. Globally the cases of gout are on the rise due to poor diet habits like fast foods and lack of physical activity [6].

Hyperuricemia happens due to lack of elimination or high synthesis of uric acid, or, a combination of the two. Under-producers consist of the majority of cases and over producers form the minority group. Under producers have altered uric acid elimination which is due to low glomerular filtration, tubular secretion, or high tubular reabsorption. The reason for over producers is either exogenous (high purine diet) or endogenous (high purine nucleotide breakdown). A minor proportion of patients can have enzymatic defects like deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) enzyme. The most common reason for combined mechanism is alcohol consumption, which leads to the breakdown of adenosine triphosphate (ATP) which generates organic acids which compete with urate for tubular secretion. Other causes are enzymatic defects such as glycogenoses type I and aldolase- B deficiency [7].

Allopurinol is very commonly used in the treatment of hyperuricemia [8]. Recommended normal dose is 200-300 mg/day. Allopurinol is ideally used in uric acid overproducers, patients with renal impairment, nephrolithiasis, or tophaceous gout and patients at risk for developing nephropathy due to high uric acid [7]. According to FACT trial, febuxostat (80/120 mg per day) was much better than allopurinol (300 mg/day) in lowering serum urate levels. Hence, febuxostat was approved by USFDA in 2009 [9]. The recommended dose is 40 mg orally once daily which can be titrated to 80 mg once daily if the desired serum uric acid levels (6 mg/dl) is not reached within two weeks [8].

NEED FOR THE STUDY

Need for the study

Both allopurinol and febuxostat are very commonly used for the treatment for hyperuricemia. In patients who have mild to moderate impaired renal function, febuxostat was better than allopurinol (at all doses) in lowering uric acid levels. Overall, febuxostat was equally safe as allopurinol in the CONFIRMS trial [10]. However, other studies (CARES trial) have identified cardiovascular events with febuxostat, and various on-going clinical trials (FAST trial) are comparing the cardiovascular safety of febuxostat versus allopurinol. In gout patients with major cardiovascular comorbidities, febuxostat equally caused adverse cardiovascular events compared to allopurinol. However, the number of cardiovascular deaths were higher with febuxostat than with allopurinol [11].

FDA has put out a statement that there is an increased risk of death with febuxostat compared to allopurinol based on a safety clinical trial that found a high-risk of heart-related death and death from all causes with febuxostat. FDA posted the latest update advising general practitioners to prescribe febuxostat only in refractory patients or who cannot tolerate allopurinol [12]. The studies so far done with febuxostat and allopurinol to compare safety and efficacy are in the western population. Extrapolating these data to other population such as South-Asians may not be pragmatic. There are no such studies performed in Indian population with febuxostat and allopurinol. Therefore, this study was designed to compare the cardiovascular safety profile of febuxostat and allopurinol in our settings.

OBJECTIVE

Objectives

- To compare the incidence of cardiovascular events with the use of febuxostat and allopurinol in patients with gout/hyperuricemia
- To compare the efficacy of febuxostat and allopurinol on lowering the uric acid levels

METHODOLOGY

Methodology

- **Study site:** Kasturba Hospital, Manipal
- **Study Design:** Retrospective cohort study
- **Study Duration:** 1 year
- **Sample size:** The retrospective cohort consists of 270 patients, out of which 174 are study cohort and 96 are control cohort. Out of 174 study cohort, 71 patients received febuxostat, 93 patients received allopurinol and 10 patients received both the drugs.
- **Ethical clearance:** Ethical clearance was obtained from Institutional Ethics Committee, Kasturba Hospital, Manipal (IEC: 479/2018) on 15th August 2018.
- **Study criteria:**

➢ ***Inclusion Criteria:***

- ❖ Patients diagnosed with gout or hyperuricemia.
- ❖ Patients who received either Febuxostat or Allopurinol for the treatment of gout.
- ❖ Both genders
- ❖ Patients above 18 years

➢ ***Exclusion Criteria:***

- ❖ Incomplete case records
- ❖ Patients with a prior history of cardiovascular diseases.
- ❖ Patients prescribed with other drugs of potential cardiovascular adverse effects

- **Materials and Methods:**

1. **Data Collection**

   In-patient medical records were collected based on the inclusion and exclusion criteria from the Medical Records Department (MRD) of Kasturba Hospital (KH), Manipal. Supplement data were obtained from an online database from KH management system (Lab Report Viewer). All the patients who received either febuxostat or allopurinol during the year 2013-2017 were selected as study cohort. For control cohort, patients who did not receive either febuxostat and allopurinol during 2013-2017 were selected from orthopedics and medicine department. These patients were retrospectively followed until 31st December 2018. The primary outcomes were cardiovascular events such as cardiovascular death, non-fatal stroke,

non-fatal myocardial infarction, urgent revascularization of unstable angina, hospitalization due to heart failure, venous thromboembolism, arrhythmia, transient ischemic attack, urgent cerebrovascular revascularization, death from any cause. These patient records were reviewed and the details were entered in a Case Report Form (Appendix 2).

2. Study materials used

Case report forms (CRF)

A suitable CRF was designed to collect the patient's data from the medical record. Various parameters like demographical details, medical history, risk factors, gout/hyperuricemia treatment parameters (drug onset, dose, frequency, usage pattern), disease outcome and follow up data were collected.

3. Statistical methods

Data analysis was performed using Statistical Package for Social Sciences (SPSS) Statistics version 20.0. Survival analysis was performed to compare the mean survival time between allopurinol and febuxostat group with cardiovascular outcomes. Paired T-test was done to compare the efficacy of each treatment within the group. Repeated measures ANOVA was performed to compare efficacy between the two groups.

4. Subject recruitment method

a. Study cohort enrolment:

Patients with gout/hyperuricemia during the year 2013-2017 were identified from the Medical Records with the help of International Classification of Diseases (ICD) coding-10. Then, the patient records were reviewed and the patients who received either febuxostat or allopurinol were selected as study cohort. The required information was collected from the patient files in the MRD and entered in the CRFs.

b. Control cohort enrolment:

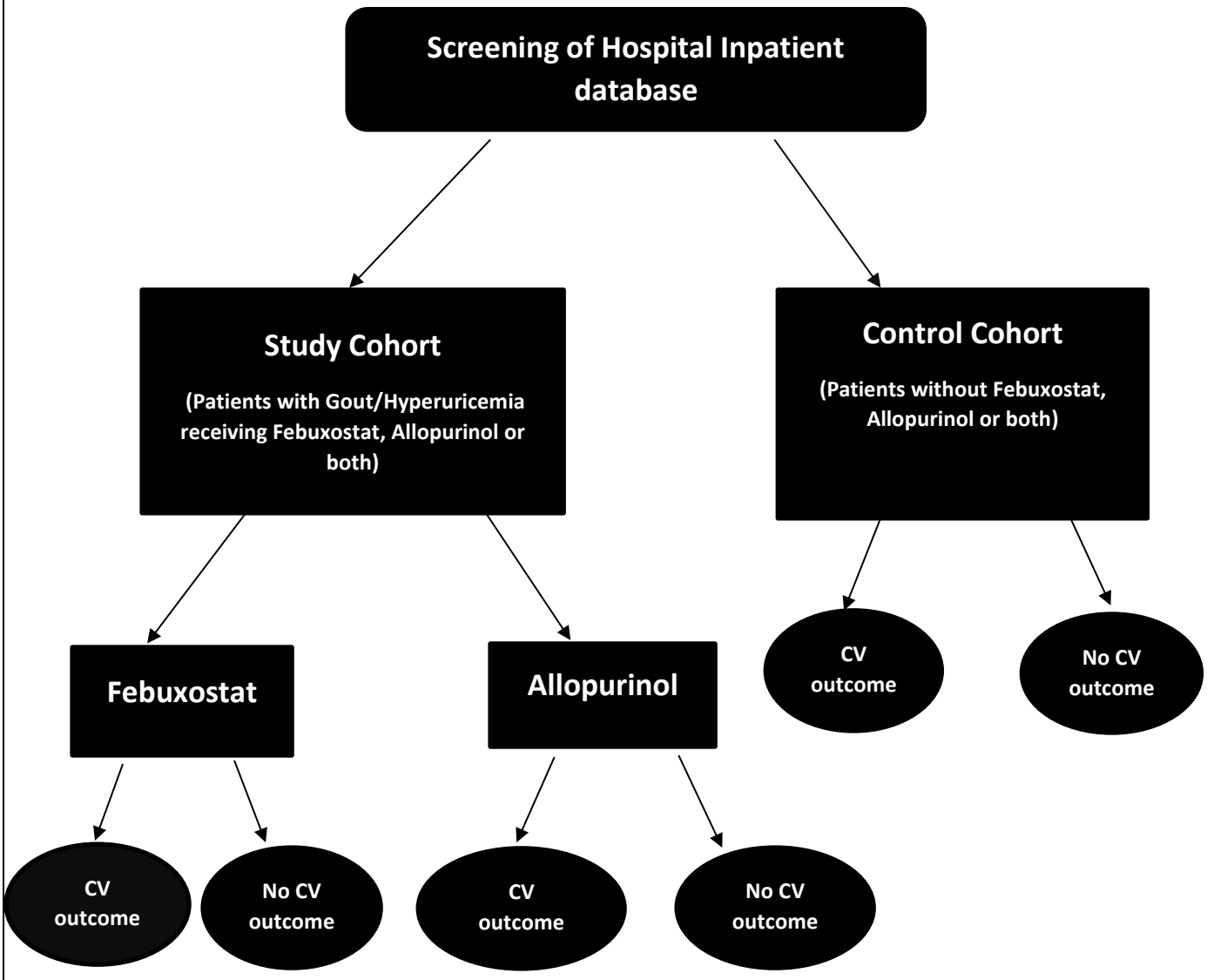
Patients who did not receive either febuxostat or allopurinol or both during 2013-2017 were randomly selected from orthopedics and medicine department of the Kasturba Hospital, Manipal. The required information was collected from the patient files in the MRD and entered in the CRFs.

5. Outcome

The primary outcome measures are the occurrence of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, urgent revascularization of unstable angina, hospitalization due to heart failure, venous thromboembolism, arrhythmia, transient ischemic attack, urgent cerebrovascular revascularization, death from any cause.

6. Study flow chart

Figure 1: Study flow chart



RESULTS

Results

1. Patient demographics overview

A total of 270 hyperuricemia/gout patients were taken for the study from 1st January 2013 – 31st December 2017. Of these, 174 hyperuricemia/gout patients were study cohort who received either febuxostat or allopurinol or both the drugs and 96 were control cohort who were randomly selected and did not receive either of the two drugs.

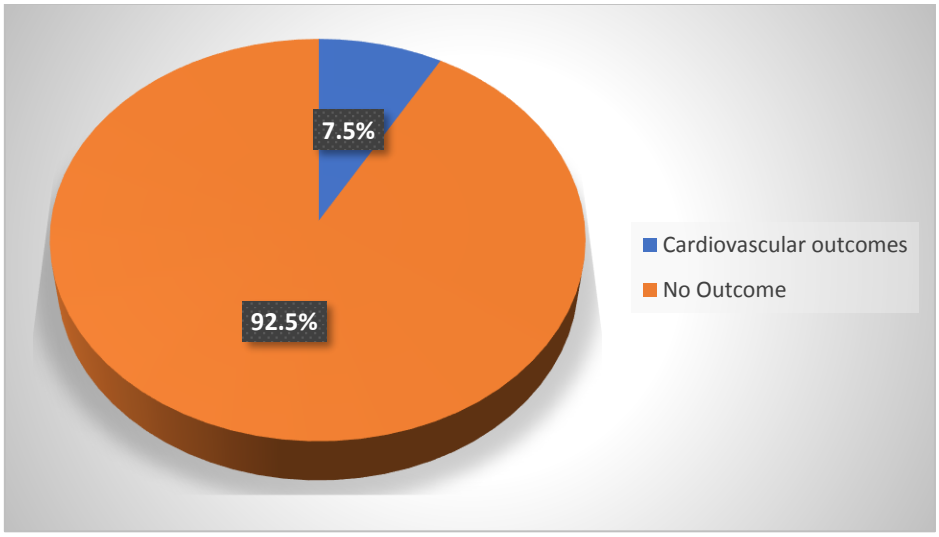
Table 1: Patient demographic characteristics

Parameters	**Study Cohort (N=174)**	**Control Cohort (N=96)**
Mean age (in years)	51	48
Gender		
Male	159 (91.4%)	62 (64.6%)
Female	15 (8.6%)	34 (35.4%)
Drug given		
Allopurinol	93 (53.4%)	----
Febuxostat	71 (40.8%)	
Both	10 (5.7%)	
Cardiovascular events		
Yes	13 (7.5%)	1 (1%)
No	161 (92.5%)	95 (99%)

In study cohort, 159 (91.4%) patients were male and 15 (8.6%) patients were female. In control cohort, 62 (64.6%) were male and 34 (35.4%) were female. Majority of the hyperuricemia/gout patients (53.4 %) received allopurinol, followed by febuxostat (40.8%). On the other hand, 5.7% study cohort patients received both febuxostat and allopurinol.

2. Incidence of cardiovascular events

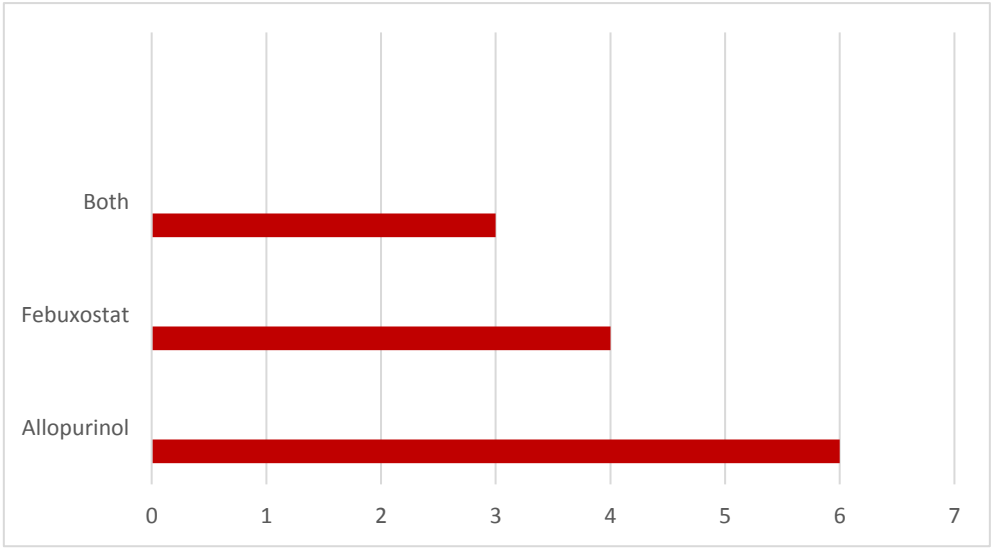
Figure 2: Incidence of cardiovascular events in study cohort



In study cohort, 13 (7.5%) patients developed cardiovascular events and 161 (92.5%) patients did not develop any cardiovascular events. In control cohort, out of 96 patients, only 1 (1.04%) patient developed cardiovascular event.

3. Incidence of cardiovascular events for each drug

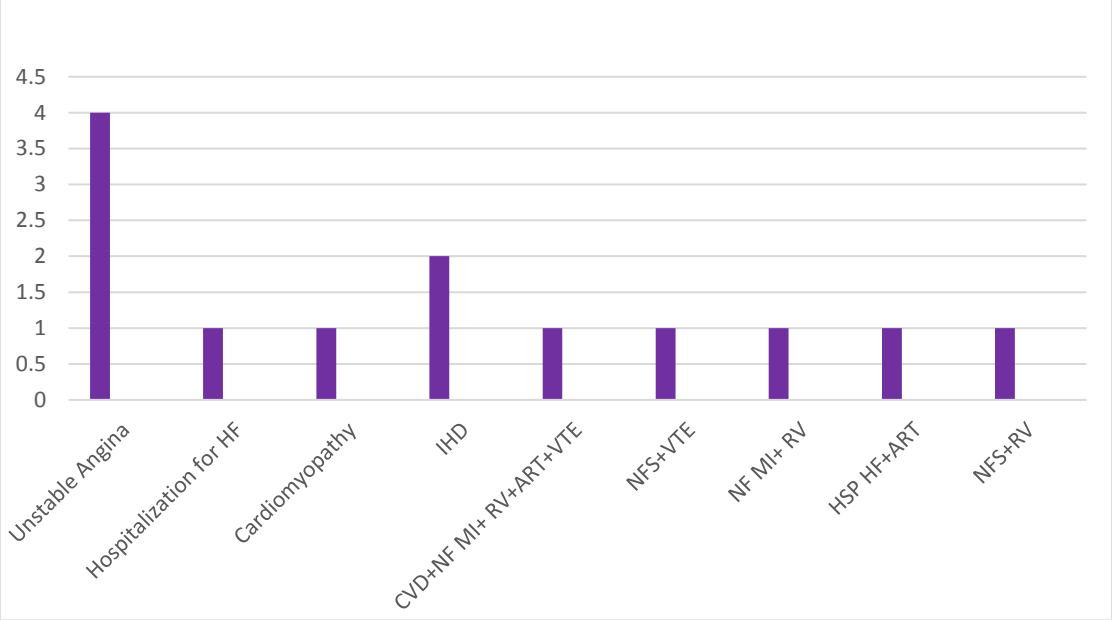
Figure 3: Incidence of cardiovascular events for each drug



Out of the 13 patients in the study cohort who had developed cardiovascular events, six patients had received allopurinol, four patients had received febuxostat and three patients had received both allopurinol and febuxostat.

4. Incidence of different cardiovascular events in the study cohort

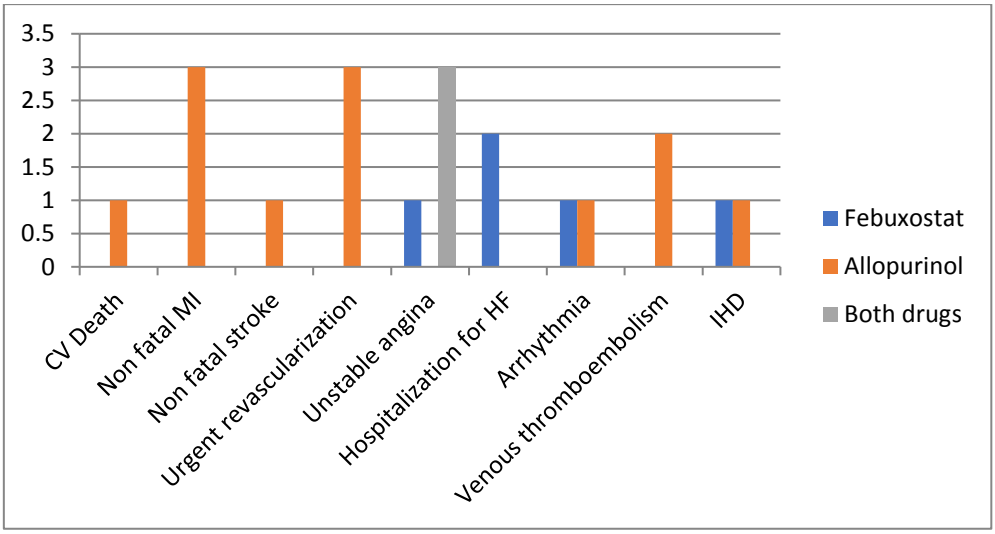
Figure 4: Incidence of different cardiovascular events in the study cohort



CVD: Cardiovascular disease; NFS: Non-fatal stroke; RV: Urgent revascularization due to unstable angina; ART: Arrhythmia; NF MI: Non-fatal myocardial infarction; HSP HF: Hospitalization for heart failure; VTE: Venous thromboembolism; IHD: Ischemic heart disease

5. Incidence of cardiovascular events based on the drugs

Figure 5: Incidence of cardiovascular events based on the drugs



6. Dose Vs Cardiovascular events

Table 2: Dose of febuxostat Vs cardiovascular events

Cardiovascular event	Dose of febuxostat		
	40 mg	80 mg	120 mg
Yes	5	0	0
No	59	9	1
Total	64	9	1

In patients who received febuxostat, 3 dose patterns were observed : 40 mg/day, 80 mg/day and 120 mg/day. All the patients who had developed cardiovascular events in the febuxostat group had received 40 mg/day.

Table 3: Dose of allopurinol Vs cardiovascular events

Cardiovascular event	Dose of allopurinol			
	100 mg	200 mg	300 mg	400 mg
Yes	1	4	**2**	**0**
No	15	45	30	1
Total	16	49	32	1

In patients who received allopurinol, 4 dose patterns were observed: 100 mg/day, 200 mg/day, 300 mg/day, 400 mg/day. Among patients who developed cardiovascular outcome, 1 patient had received 100 mg/day dose, 4 patients received 200 mg/day and 2 patients received 300 mg/day.

7. Number needed to harm (NNH)

Table 4: Number needed to harm for cohort study

Study population	Cardiovascular events	No cardiovascular events	Total
Study Cohort	13	161	174
Control Cohort	1	95	96
Total	14	256	270

NNH = 1/ Incidence in exposed- Incidence in non-exposed
= **15.625 ~ 16**

This indicate that every 16 patients who received febuxostat / allopurinol or combination, one patient developed cardiovascular events.

Table 5: Number needed to harm for Febuxostat

Study population	Cardiovascular events	No cardiovascular events	Total
Febuxostat group	4	67	71
Control group	1	95	96
Total	5	162	167

NNH = 21.73 ~ 22

This indicate that every 22 patients who received febuxostat, one patient developed cardiovascular events.

Table 6: Number needed to harm for Allopurinol

Study population	Cardiovascular events	No cardiovascular events	Total
Allopurinol group	6	87	93
Control group	1	95	96
Total	7	182	189

NNH = 18.51 ~ 19

This indicate that every 19 patients who received febuxostat, one patient developed cardiovascular events.

Table 7: Number needed to harm for patients who received both drugs

Study population	Cardiovascular events	No cardiovascular events	Total
Both	3	7	10
Control group	1	95	96
Total	4	102	106

NNH = 3

This indicate that every 3 patients who received both the drugs, one patient developed cardiovascular events.

8. Survival analysis

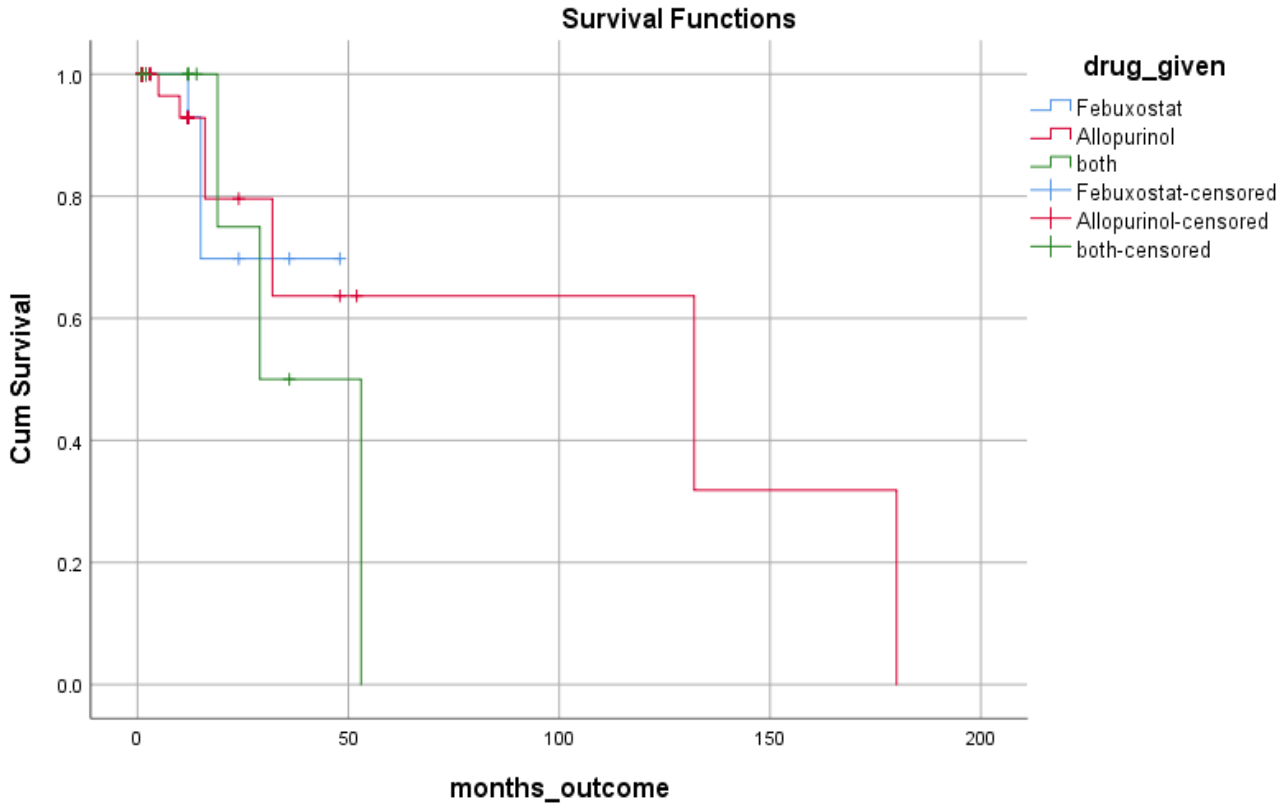
Table 8: Comparative survival analysis of the drugs

Drug given	Mean (in months)	95% CI		*p* value*
		Lower	Upper	
Febuxostat	37	24	51	0.762
Allopurinol	107	52	162	
Both	38	20	56	

CI: Confidence Interval; *p*: Probability; * Kaplan meier analysis

The mean survival time for febuxostat was found to be lesser (37 months) than allopurinol (107 months) and both the drugs (38 months).

Figure 6: Comparative survival analysis of the drugs



9. Comparative efficacy of febuxostat and allopurinol

Table 9: Change in serum urate levels in febuxostat group and allopurinol

Drugs	Measures	Initial serum urate level (mg/dl)	Final serum urate level (mg/dl)
Febuxostat	Mean	8.992	6.237
	SD	2.211	2.062
Allopurinol	Mean	7.984	6.847
	SD	1.903	1.732

SD: Standard Deviation

Table 10: Comparative efficacy of febuxostat and allopurinol in reduction of serum urate level

Drugs	Mean Difference	95% CI		*p* value*	Percentage reduction
		Lower	Upper		
Febuxostat	2.754	2.209	3.299	0.000	30.6%
Allopurinol	1.137	0.792	1.482	0.000	14.2%

CI: Confidence Interval; *p*: Probability *Paired T test

The mean difference of the initial and final serum urate level for febuxostat and allopurinol is 2.754 mg/dl [p=0.000; CI(95%) 2.209-3.229] and 1.137 mg/dl [p=0.000; CI(95%) 0.792-1.482] respectively. *Both the drugs showed a significant reduction in serum uric acid levels. The percentage reduction for febuxostat was 30.6% and allopurinol was 14.2%.*

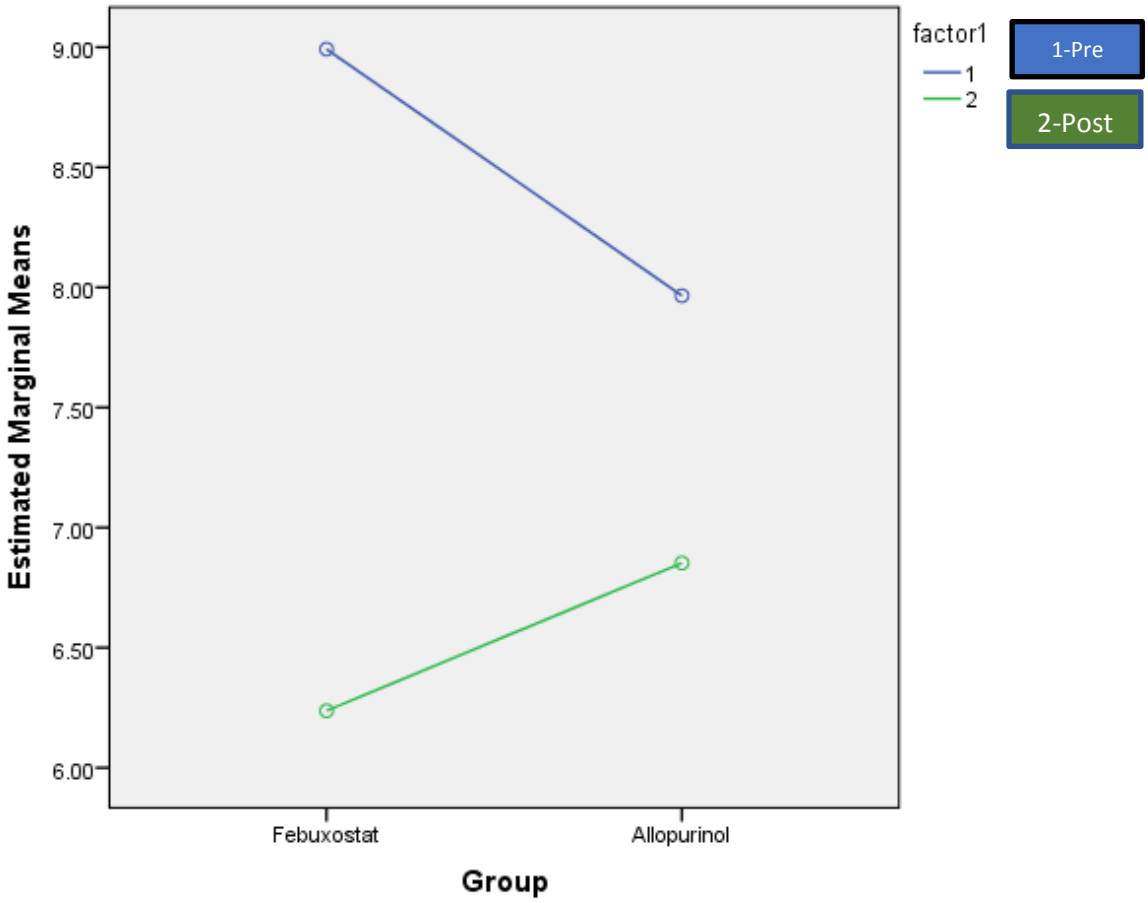
Table 11: Comparative efficacy in between the drug groups using repeated measures ANOVA

Source	f value	*p* value*
Group	0.632	0.428

f: ratio of between-groups to within-groups variances ; *p*: Probability; *Repeated measures ANOVA

There was no significant difference between allopurinol and febuxostat group in lowering the serum urate levels.

Figure 7: Comparative reduction of serum urate levels in Febuxostat & Allopurinol (Pre and Post



DISCUSSION

Discussion

In our study, cardiovascular events were seen in 13 patients out of 174 cases. 4 out of 71 patients were in (5.63%) in febuxostat group, 6 out of 93 patients (6.45%) in allopurinol group and 3 out of 10 patients (30%) in the group receiving both drugs. Whereas in CARES trial, the primary end-point event (same as the cardiovascular events included in our study) occurred in 335 patients (10.8%) in febuxostat group and in 321 patients (10.4%) in the allopurinol group [11]. In our study, there was one cardiovascular death in allopurinol group. Whereas in CARES trial, cardiovascular deaths were higher in the febuxostat group than in the allopurinol group [11]. However, we cannot conclude on this as the sample size was not equal in between the groups (71 for febuxostat group and 93 for allopurinol group).

There were no previous studies done for estimating the mean survival time of febuxostat and allopurinol and number needed to harm (NNH). Therefore, we have included these two parameters in our objective. In our study, we found the mean survival time for febuxostat to be 37 months [CI (95%) 24-51], which is lesser than both the allopurinol group i.e. 107 months [CI (95%) 52-162] and the group receiving both drugs i.e. 38 months [CI (95%) 20-56]. However, there was no significant difference found between the two (p=0.762). This might be due to less sample size in our study. We also found the number needed to harm for febuxostat to be 19, 22 for allopurinol and 3 for group receiving both the drugs.

In our study, the mean difference of the initial and final serum urate level for febuxostat was 2.754 mg/dl [p=0.000; CI (95%) 2.209-3.299] and for allopurinol it was 1.137 mg/dl [p=0.000; CI (95%) 0.792-1.482]. Both of the drugs were efficacious in reducing serum urate levels. However, we did not observe a significant difference between the drugs in reducing serum urate levels. Similarly, CONFIRMS trial concluded equal efficacy for both febuxostat (40 mg) daily and allopurinol (300/200 mg) daily in lowering serum urate levels. But they found at all level of renal function, febuxostat (80 mg) was more efficacious to both febuxostat (40mg) and allopurinol (300/200 mg) and was comparatively safer to use. Whereas in mild or moderate renal impairment, febuxostat 40 mg daily was significantly much better in lowering serum urate than allopurinol [10]. On the other hand, the FACT trial reported that febuxostat (80/120 mg per day) was much better than allopurinol (300 mg per day) in lowering serum urate levels [13].

CONCLUSION

Conclusion

- ✓ Our study shows that both febuxostat and allopurinol are significantly efficacious in reducing serum urate levels, but we could not compare efficacy between the two groups probably due to low sample size.
- ✓ Our study shows that both febuxostat and allopurinol cause increased risk of cardiovascular events with chronic use. Incidence of cardiovascular events was more in allopurinol group than in febuxostat group.
- ✓ The mean survival time is lesser in febuxostat than allopurinol.
- ✓ Due to low sample size and a minimal number of outcome events we could not conclude on other confounding factors involved.
- ✓ Therefore, these drugs must be prescribed with caution and should be monitored in patients who already have risk factors for developing cardiovascular diseases. Patients should inform the doctors if they already have some cardiovascular ailments/history of some kind and report any kind of symptoms experienced after the use of these drugs immediately.

LIMITATIONS OF THE STUDY

Limitations of the study

The following are the limitations:

- The current study is done on a small sample size in a single center. Therefore, the result of the study cannot be generalized throughout the population.
- Since the study is a retrospective design, there is a limitation for data availability and high volume of missing data. Hence the accuracy of the data is uncertain.
- Patients with cardiovascular risk factors were also included in study cohort, but the hazard ratio for the risk factors related to the end point could not be calculated due to less number of outcome.

FUTURE DIRECTIONS

Future directions

- A multicentric randomized controlled study should be performed to determine comparative safety and efficacy of allopurinol and febuxostat.
- Impact of different doses of allopurinol and febuxostat on clinical and biochemical improvement in hyperuricemia/gout patients.

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APPENDICES

APPENDIX - 1

KASTURBA HOSPITAL
MANIPAL
(An associate Hospital of MAHE, Manipal)

Kasturba Medical College and Kasturba Hospital
Institutional Ethics Committee
(Registration No. ECR/146/Inst/KA/2013/RR-16)

Communication of the decision of the Institutional Ethics Committee

Wednesday 15th August 2018 **IEC : 479/2018**

Project title	:	Cardiovascular Safety of Febuxostat and Allopurinol in Gout/Hyperuricemia Patients: A Retrospective Cohort Event Reporting in a Tertiary Healthcare Facility.
Principal Investigator	:	Miss. Sushmita Sharma
Guide/ Co Guide/ Co Investigators	:	Dr. Sonal Sekhar M, Dr. Anil K. Bhat, Angsheeta Chakraborty
Name & Address of Institution	:	Department of Pharmacy Practice, MCOPS, MAHE, Manipal, Department of Orthopedics, KMC, MAHE, Manipal. Department of Pharmacy Practice, MCOPS, MAHE, Manipal.
Status of review	:	New
Date of review	:	14.08.2018
Decision of the IEC	:	Approved for the study period from 14.08.2018 to 13.08.2019 as mentioned in protocol.

- The PI and all members of the project shall ensure compliance to current regulatory provisions (as per Schedule Y of Drugs and Cosmetics Act and ICH-GCP), Ethical Guidelines for Biomedical Research on Human Participants by ICMR, and the SOP of IEC including timely submission of Interim Annual Report and Final Closure Report
- Participant Information Sheet and a copy of signed Informed Consent shall be given to every research participant
- Inform IEC in case of any proposed amendments (change in protocol / procedure, site / Investigator etc)
- Inform IEC immediately in case of any Adverse Events and Serious Adverse Events.
- Members of IEC have the right to monitor any project with prior intimation.

Dr. Stanley Mathew
MEMBER SECRETARY - IEC

INSTITUTIONAL ETHICS COMMITTEE APPROVED KASTURBA HOSPITAL, MANIPAL

IEC Secretariat, Room No. 22, Ground Floor, Faculty Room Complex, Kasturba Medical College Premises,
Kasturba Medical College, Manipal - 576104, Karnataka, India. Phone : +91 - 0820 - 2933522,Fax : +91 - 0820 - 2571927. Email : iec.kmc@manipal.edu

MR-798

(Yoga and Ayurveda services are excluded from the scope of NABH accreditation)

APPENDIX - 2

PATIENT DOCUMENTATION FORM

DEMOGRAPHIC DETAILS

IP No:	HP No:	Fam History:	M/F :
Occupation:	Height:	Age	
Contact No:	Weight:	BMI	

MEDICAL HISTORY

Body System	Diagnosed Condition?	Diagnosis/Surgery	Onset Year/ Date	Current Problem

Additional Info :

RISK FACTORS/EXPOSURES:

Condition/Exposure	Present (Y/N)	Onset and additional info
Diabetes Mellitus (with small vessel disease)		
Hypertension		
Hyperlipidemia		
Peripheral vascular disease		
Smoking		
Alcohol		
Family history + Psychosocial factors		

GOUT/HYPERURICEMIA PARAMETERS

Onset :	Serum urate level:	

DRUG

FEBUXOSTAT ◯ ALLOPURINOL ◯ OTHERS :

Onset	Dose	Cardiotoxic drugs
Frequency	Usage pattern	

TESTS

Breathlessness ◯ Dyspnea ◯ Orthopnea ◯ DOE ◯ EF < 40% ? ◯ E/A:

Doppler Test: BNP: Troponin:

ECG :

DISEASE OUTCOME

DISEASE	Y/N + ONSET	DISEASE	Y/N + ONSET
CV Death		Transient ischemic attack	
Non fatal MI		Hospitalization for HF	
Non fatal stroke		Arrhythmia	
Urgent revascularization due to unstable angina		VTE	
Death from any cause		Urgent cerebrovascular revascularization	

FOLLOW UP OUTCOME

Completed ◯ Loss of FU ◯ Death ◯ DAMA ◯

APPENDIX – 3

Plagiarism report

Cardiovascular safety of Febuxotat and Allopurinol in gout/hyperuricemia patients

ORIGINALITY REPORT

11%	6%	9%	2%
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PRIMARY SOURCES

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6	AM Carella. "Hyperuricemia and global	1