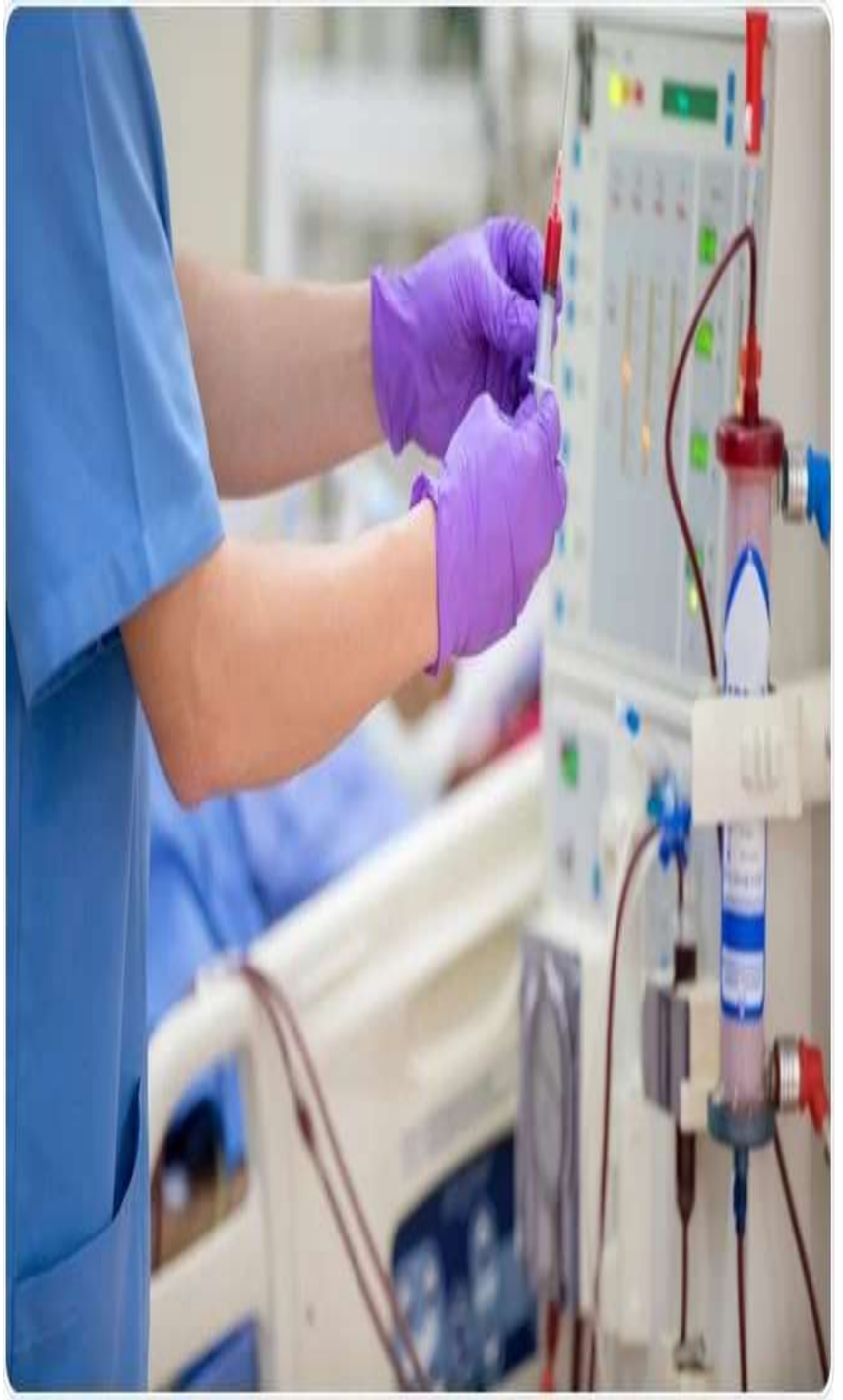
بسم الله الرحمن الرحيم

Effect of Cinacalcet on Secondary hyperparathyroidism in Patients With Chronic Kidney Disease Undergoing Dialysis in Al-Mana General Hospital (AGH), Kingdom of Saudi Arabia

Riad Mohammed Abdelrahman
Assistant Professor of Clinical Pharmacy
Faculty of Pharmacy-Libyan International Medical University Benghazi-Libya



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Study background

- Chronic kidney disease (CKD) complications are leading cause of mortality.
- Management of sHPT ;↑ PTH, ↑ phosphorus, and ↓ calcium levels is important in slowing progression of CKD.
- The Kidney Disease: Improving Global Outcomes (KDIGO) is most commonly used treatment guidelines for management of CKD.
- The calcimimetics; CaSR modulators, recommended by KDIGO for resistant sHPT (Cinacalcet approved by (FDA) in 2004 to treat sHPT in CKD).

Significant of study

- Chronic Kidney Disease (CKD) is increasing in prevalence → diabetes & Aging.
- CKD population suffers a high mortality mainly due to cardiovascular diseases.
- Achieving targets is difficult ; Limitations of the conventional therapies.
- Cinacalcet in 2004; Positive impact on mortality in CKD patients.
- A heated debate arose in 2012 following the publication of The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, which fails to demonstrate the clinical usefulness of cinacalcet.

- The EVOLVE trial results were disappointing to clinicians and patients alike; despite this, clinicians continue to prescribe the drug, and patients continue to take it.
- Both groups need a clearer, objective understanding of the balance between risks and benefits.
- The **purpose** of this study is to evaluate the role of cinacalcet in managing sHPT and CKD-MBD, especially the clinical outcomes, and to shed light on and offer evidence for the beneficial effect of cinacalcet, behind that we aim to shorten the gap between the Global Guidelines and the local natural life practices regarding CKD-MBD management.

Objectives

1. This study investigates the impact of cinacalcet add-on therapy on the:

    A. Biochemical profile:

        1. Mean percentage change from baseline in PTH levels

        2. Proportion of participants with plasma PTH <300 pg/ml

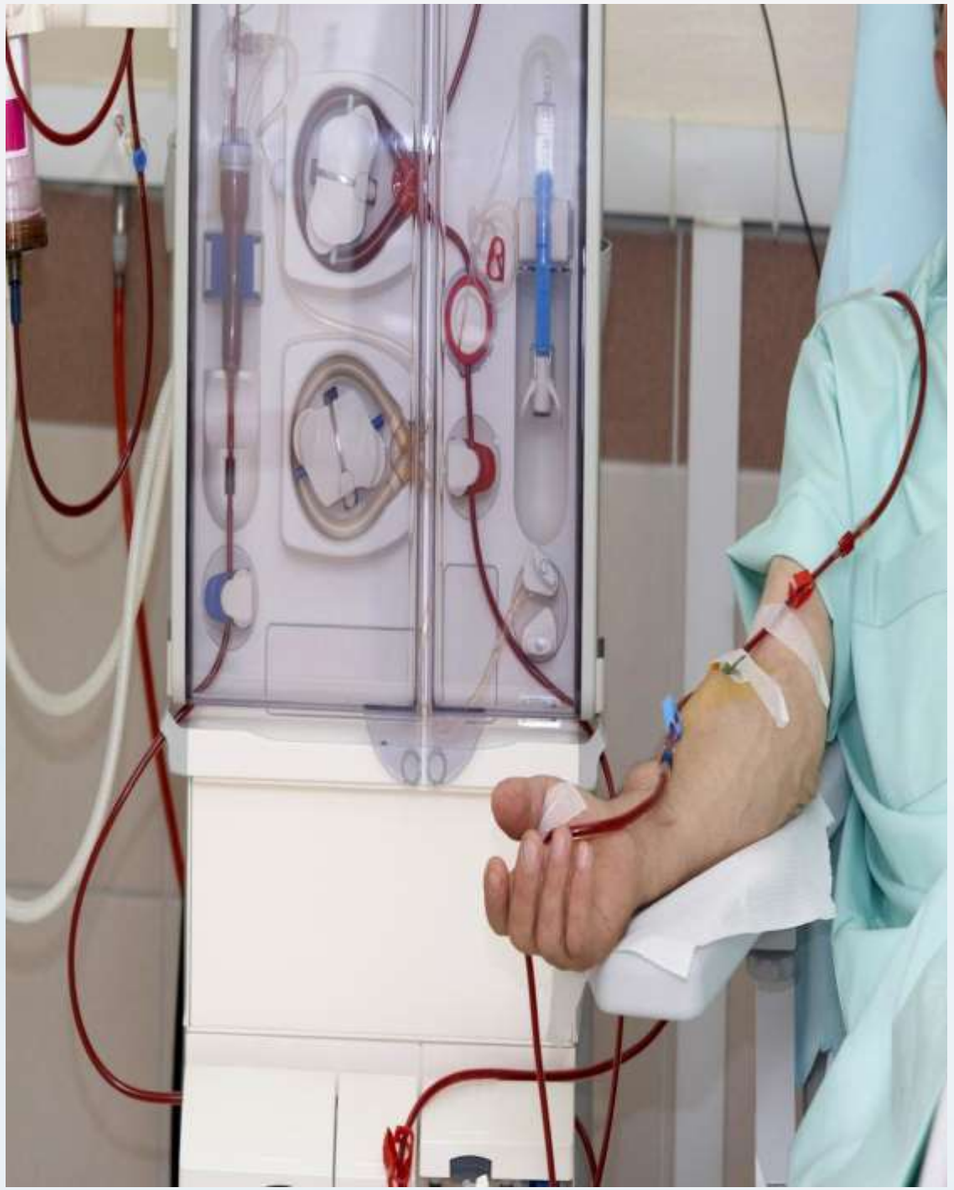
        3. Proportion of participants with a ≥30% decrease from baseline in PTH.

    B. Clinical outcomes :

        Incidence and (time to event) of cardiovascular events and mortality (All-cause and cause-specific) and bone fracture.

2. This study assesses the safety of Cinacalcet, including its nature and frequency..

3. This study determines cinacalcet effect modifiers, the following factors were prespecified for subgroup analysis: age, age ranking (<65 and ≥65 years), gender, CKD etiology, and baseline plasma PTH



Patients &Methods

Study design

- A mixed retrospective/prospective cohort multicenter study in sHPT-CKD patients on haemodialysis.

Study population

- 261 patients were initially screened.
- 174 subjects included in the final evaluation.

Study intervention

- According to the local guidelines in nephrology unit at AGH.
- Cinacalcet group (n=60) ,a conventional therapy group (n=114).

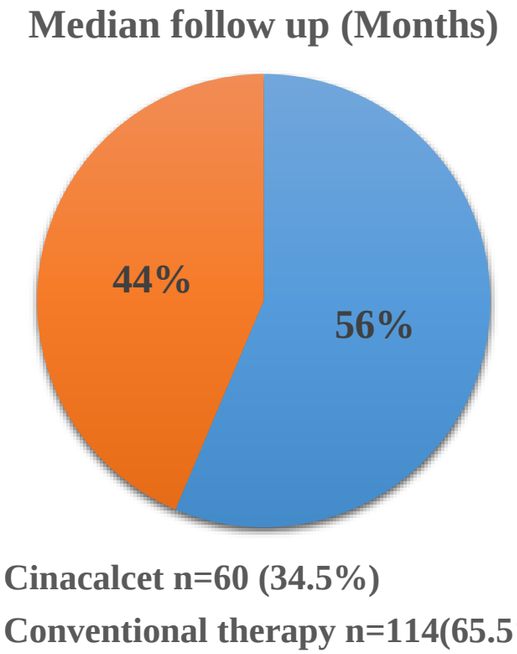
Data collection: Biochemical & clinical profile collected initially & after EAP(6 months)

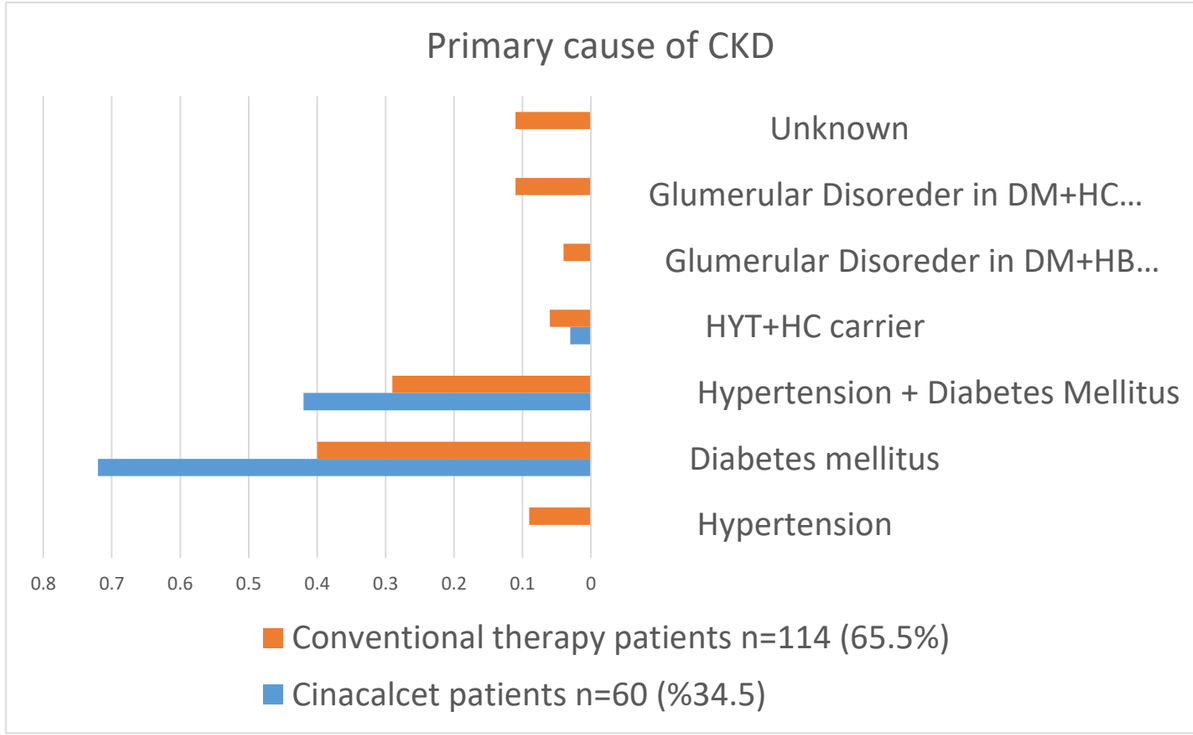
Statistical analysis:

- Kolmogorov– Smirnov Z test used for normality testing.
- Levene’s Test for Homogeneity of Variance.
- Differences between groups and sub-groups were determined using the Mann-Whitney U test (continuous variables) or the Chi-Square test (discrete variables).
- **Kaplan-Meier**, time-to-event curves for crude and adjusted analyses for cardiovascular event endpoints and mortality ,The Log Rank (Mantel-Cox) test was used .The HR and 95% CIs were calculated using **Cox proportional-hazards regression models** to provide a relative event rate between groups and subgroups.
- Significance ; (≤ 0.05) was considered.

Results

- None of the variables was normally distributed →median and percentiles.
- Patients were followed for a median follow-up of 12(IQR 12; 16) months in the total sample.
- The median age of the patients was 61 years in the total sample (IQR 57; 73),
- Etiology of CKD in 89(51%) was Diabetes mellitus, followed by Hypertension + Diabetes Mellitus 58 (33%).





Participant demographics and baseline characteristics (Total n=174)

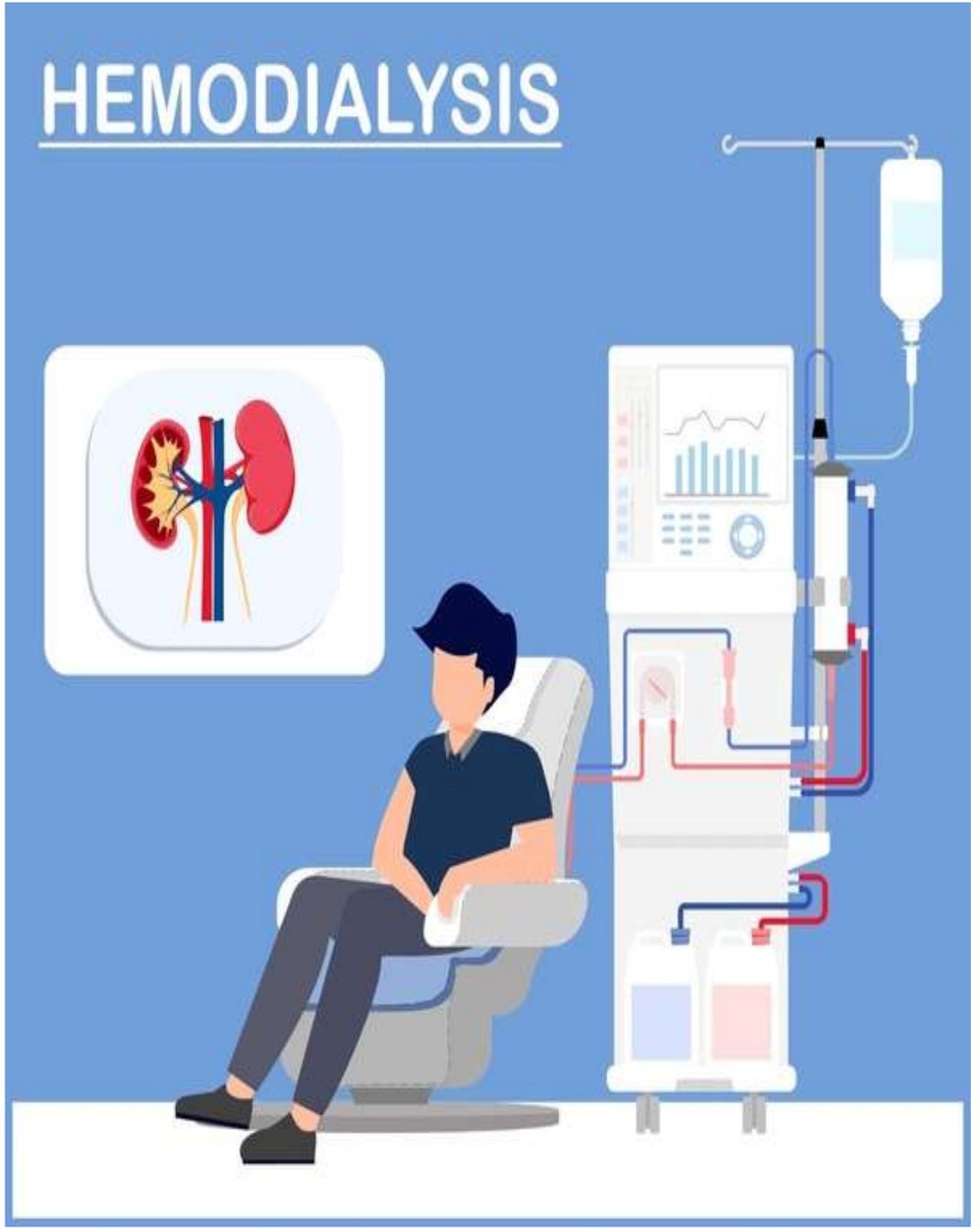
Variable	Cinacalcet median (25th;75th percentile)	Conventional therapy median (25th;75th percentile)	p-value
Age (years)			
Median	60.5(55.25,73.25)	62(57,73)	0.50
Max	90	88	
Min	42	42	
Age ranking			0.16[a]
Young	37(62%) ±0.5	63(55%) ±0.5	0.52
Older	23(38%) ±0.5	51(45%)± 0.5	0.44
Gender			0.002
Males	42(70%) ±0.46	71(62%)± 0.49	0.49
Females	18(30%)±0.46	43(38%) ±0.49	0.33
Median Follow-up(Months)	15.5(12,19)	12(9.75,12)	0.000
Median GFR(ml/min)	9.6(8.51,11.48)	9.9(8.88,11.50)	0.325

Results

1. Impact on Biochemical Parameters

Primary endpoints

- The study revealed significant improvements in biochemical parameters in the cinacalcet add-on group compared to the conventional therapy group.
- The mean percentage change in iPTH was significant for the cinacalcet group compared to the conventional therapy group (p-value: 0.004).
- Males and older patients significantly respond better for cinacalcet (p-value: 0.01& 0.03 respectively).



Secondary endpoints

1 iPTH Reduction

Cinacalcet was more effective in achieving a ≥30% reduction in iPTH (p-value 0.003).

2 iPTH Levels

Cinacalcet was more effective in achieving iPTH levels ≤300 pg/ml (p-value 0.025).

Exploratory endpoints

3 Serum Calcium

Median serum calcium increase was not significant (p-value: 0.17).

4 Serum Phosphorus

Median serum phosphorus decreased significantly (p-value: 0.009).

2. Impact on Cardiovascular Events

- Significant reduction in the frequency of cardiovascular events (p-value 0.02).

	Total patients (n=174)	Cinacalcet (n = 60)	Conventional (n = 114)	P-value Chi-square
Cardiovascular events(all)	63(36%)	14(23%)	49(42%)	0.02
First Cardiovascular events	53(30%)	10(17%)	43(38%)	0.005

Clinical outcomes; frequency of cardiovascular events-All & First Cardiovascular events

Kaplan-Meier time to event analysis

Cox proportional analysis

1

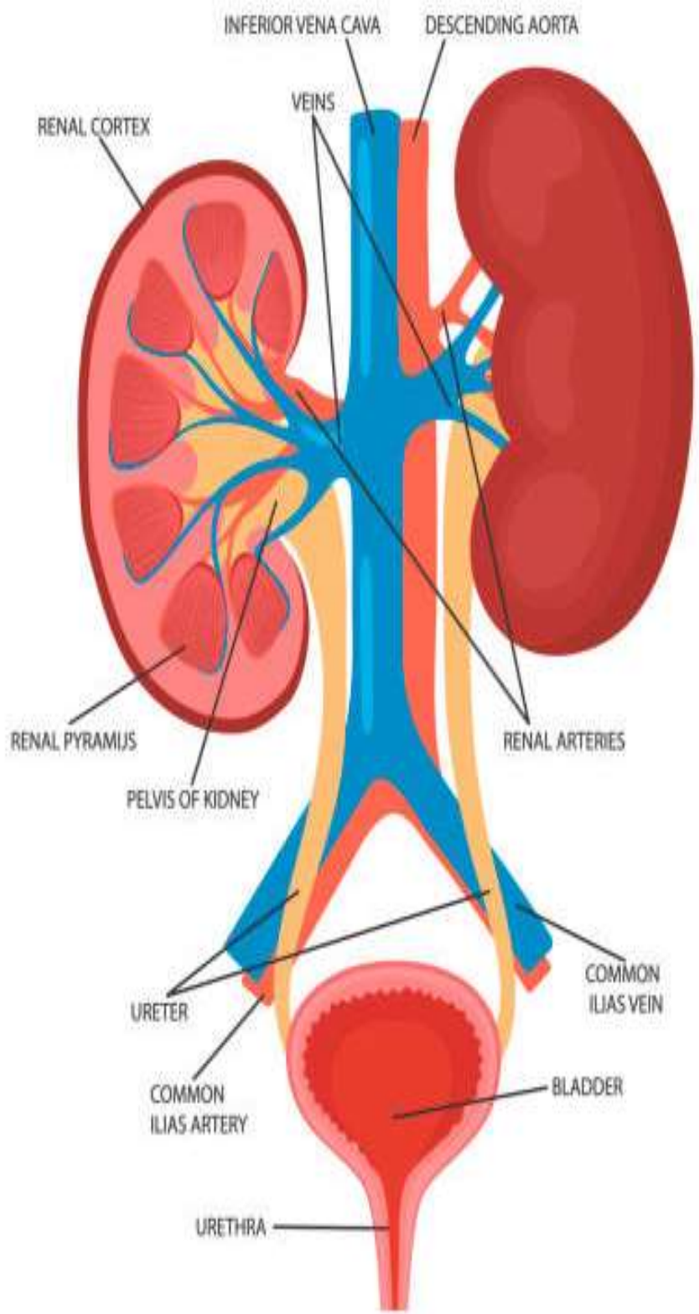
2

Cause –specific /IHD/Unstable Angina/MI

There was a significant delay in the incidence of IHD/Hospitalization for Unstable Angina/MI in the cinacalcet group compared to the conventional therapy group (p=0.04).

All-Cause Hospitalization

Cinacalcet add-on patients were 79% less likely to experience all-cause hospitalization; HR 0.31 (95% CI: 0.16-0.63), p-value: 0.001.



3. Impact on Mortality

(All-Cause Mortality and CV Mortality)

1

No significant difference was observed in the crude frequency of all-cause mortality or CV mortality between the two groups (p-value: 0.52 & 0.87, respectively).

3. Impact on Mortality

However ,when adjusted for etiology of CKD, Cinacalcet showed a lower mortality rate in patients with HYT or HYT+DM2.

2

HYT Aetiology
HR 0.46 (0.21-1.00, p=0.05)

3

HYT+DM2 Aetiology
HR 0.42 (0.2-1.00), p=0.04

4. Impact on Bone Fractures

- No significant difference in the frequency of bone fractures (p-value 0.26).
- However, a trend towards protection against the risk of fractures was observed in males and older patients(Gender; HR 0.22, 95% CI: (0.03 - 2.02), p-= 0.2, Age ranking; HR 0.53, 95% CI: (0.014- 17.8), p-value 0.7). .

5. Cinacalcet Safety

Hypocalcemia

Hypocalcemia Incidence	Hypocalcemic Events
No significant difference (p-value 0. 37)	Significant difference (p-value 0.017)

Nausea and vomiting

- The study found that cinacalcet significantly caused nausea and vomiting (p-value 0.000 & 0.008, respectively).
- This highlights the importance of monitoring for these side effects in patients receiving cinacalcet therapy.

Conclusion

- The study concluded that cinacalcet-based treatment is superior in achieving most of the K/DIGO biochemical targets for patients with CKD-SHPT under HD, especially in males and older patients.
- Cinacalcet effectively reduces cardiovascular events, particularly IHD/Unstable angina/MI, especially in males and older patients.
- However, cinacalcet is not effective in reducing the risk of all-cause and cardiovascular mortality, except in patients with HYT or HYT+DM2 etiology.
- Cinacalcet might increase the average number of hypocalcemic events, nausea, and vomiting.

Study Limitations

- Limitations included are the observational design and short period of follow-up (12 months, which is unlikely to be sufficient for the detection of substantial changes in vascular calcification and consequent cardiovascular complications).
- Although this study was not an RCT ,it may be more representative of “real life situations”, data were derived randomly from a number of Al-Mana hospital; therefore, it may be appropriate to extrapolate the results to the general population of CKD patients.

Recommendations & Future Research

1. Our findings supports physicians in planning therapeutic strategies for sHPT management in CKD in individual dialysis patients.
2. Our research suggests that, cinacalcet add-on regimen should be used to improve the biochemical profile (especially in males and older patients) in which conventional therapy alone is not effective.
3. We suggests that cinacalcet add-on regimen should be used in patients with high risk of incidence of cardiovascular events and in patients with HYT and HYT+DM2 etiology.
4. We recommend that patients taking cinacalcet should be appropriately counselled because of the high adverse event profile of this drug (cinacalcet may increase the risk of some gastrointestinal side effects).

Future trials are required to confirm and expand our results


THANK YOU!