

Prophylactic Add-on Antiplatelet Therapy in Chronic Kidney Disease with Type 2 Diabetes Mellitus: Comparison Between Clopidogrel and Low-dose Aspirin

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ABSTRACT

Background: Chronic kidney disease (CKD) coexisting with type 2 diabetes mellitus (DM) leads to coronary artery disease. The present study compares clopidogrel and low-dose aspirin as prophylactic therapy against coronary events in patients with CKD with diabetes.

Methods: Total 80 patients of CKD with type 2DM were randomized and allocated to clopidogrel and aspirin groups to receive the drug at a dose of 75 mg and 150 mg once daily respectively for 8 weeks as add-on therapy. Main outcome was change in blood pressure, metabolic parameters, renal function, inflammatory biomarkers, platelet aggregability and (UKPDS) United Kingdom Prospective Diabetes Study risk scoring.

Results: Significant decrease in blood pressure ($P < 0.01$), total cholesterol ($P = 0.02$), LDL ($P < 0.01$), triglyceride ($P < 0.01$) and a better glycemic control ($P < 0.01$) was found in clopidogrel group. Renal markers and electrolytes have been improved in clopidogrel group but in aspirin group there was deterioration (2.5%) of creatinine clearance. Clopidogrel group has shown a significant decrease in hsCRP ($P < 0.01$), UKPDS risk scoring ($P < 0.01$) and better anti-aggregatory effect.

Conclusions: Clopidogrel has prophylactic role in CKD with type 2 DM due to better control of metabolic parameters, renal function and inflammatory burden in comparison to aspirin.

Keywords: Chronic kidney disease, clopidogrel, low-dose aspirin, type 2 diabetes mellitus

INTRODUCTION

Chronic kidney disease (CKD) has emerged as a major public health problem of primary importance especially in developing countries.^[1] The presence of CKD is one of the most potent known risk factors for cardiovascular disease (CVD). Individuals with CKD have a 10- to 20-fold greater risk of cardiac death, mainly because of the high risk for coronary heart disease and other cardiovascular complications, which virtually coexists with diabetes, hypertension, obesity, lipid

abnormalities, hyperaggregability state and endothelial dysfunction.^[2,3] CKD in the presence of other co-morbidities like type 2 diabetes mellitus and hypertension can lead to early progression to end-stage renal disease (ESRD or stage V CKD), which confers a greater risk for CVD morbidity and mortality. Cardiovascular events are the leading cause of premature death in patients with CKD even before their progression to ESRD.^[4]

The correlation between raised serum creatinine levels and CVD mortality was first observed by Shulman *et al.*, in 1989 in the Hypertension Detection and Follow-up Programme study.^[4] This concept received wide attentions in 2003 after the scientific statement from the American Heart Association endorsed the fact that increased CVD mortality is noted in patients of CKD when compared with the general population.^[5] This begins in the early stages of renal impairment and rises continuously to 20 to 30 times above that in the general population, as the renal damage progresses to ESRD.^[6]

Antiplatelet drugs have an established place in the prevention of vascular events in a variety of clinical conditions, such as myocardial infarction, stroke and cardiovascular death.^[7-10] Very few studies have been done regarding effect of antiplatelet therapy on renal function and warrants further studies. In First United Kingdom Heart and Renal Protection (UK-HARP-I) study the safety of low-dose aspirin was done on patients of chronic kidney disease.^[11] Deray G *et al.*, looked for clopidogrel activities in patients with renal function impairment.^[12,13] Clopidogrel 75 mg once daily was well-tolerated in patients with both moderate or severe renal failure, and provided good inhibition of ADP-induced platelet aggregation without excessive extension of bleeding time. Though aspirin is encouraged in all patients with CKD the therapeutic use of clopidogrel has not been predominant due to its far greater cost compared to aspirin.^[14] However, the overall hospital care cost of chronic kidney disease with risk of cardiovascular disease may be far in excess. Hence rethinking is mandatory to reassess efficacy, safety, convenience promised by clopidogrel versus risks and benefits associated with aspirin. The present one is a comparative clinical study of aspirin versus clopidogrel in cardiovascular prophylaxis in patients with renal dysfunction under primary

nephrology specialty care to generate evidence base for rational therapeutic practice.

METHODS

Subjects

Patients ($n = 80$) of chronic kidney disease (Serum Creatinine level ≥ 1.8 mg/dl) with type 2 diabetes mellitus aged 50 years and above were recruited from the Department of Nephrology, Sir Sunderlal Hospital, Banaras Hindu University, Varanasi, India. Patients having underlying peptic ulcer disease, gastrointestinal bleeding, bleeding disorders, gout, chronic liver disease, asthma, underlying infection/sepsis; or on therapy with anticoagulants, NSAIDs, anti-hypertensives or any antiplatelet therapy within 2 months were excluded.

Study design

The present study is an 8-week, randomized, open, parallel group comparative clinical study between clopidogrel and low-dose aspirin in patients with chronic kidney disease with type 2 diabetes mellitus conducted in a single centre. The study was approved by Institute Ethical Committee and procedures followed in this study are in accordance with the ethical standard laid down by ICMR's ethical guidelines for biomedical research on human subjects (2006). A written informed consent was taken from all the patients participated in the study after explaining the patient's diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of a proposed add-on treatment (clopidogrel/low-dose aspirin). Randomization was done by using computer-generated random list. After taking written informed consent and baseline clinical evaluation, clopidogrel was prescribed to 40 patients at a dose of 75 mg once daily orally and aspirin was prescribed to another 40 patients at a dose of 150 mg once daily orally for 8 weeks as add-on therapy to the standard therapeutic regimen (therapy as per discretion of the nephrologists). The sample size has been calculated considering hsCRP as primary outcome, expected mean difference of 0.5 and power of the study being 0.80. After 8 weeks, clinical parameters were re-evaluated

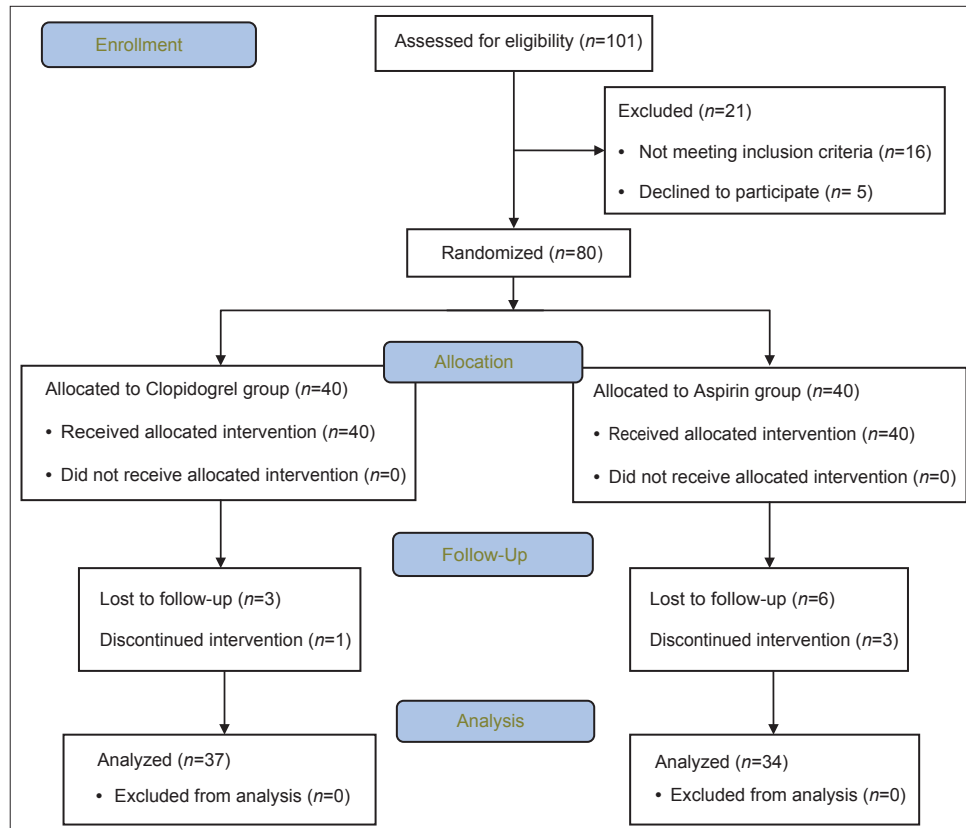


Figure 1: Recruitment, allocation and follow-up of participants abstract

and statistically analyzed. Total 71 patients (37 in clopidogrel group and 34 in aspirin group) completed this study. Nine patients were lost to follow-up [Figure 1].

Efficacy variables

The efficacy variables were change from baseline to day 56 in blood pressure, glycemic control (fasting and postprandial, HbA_{1c}), Lipid profile, Inflammatory biomarkers (hs C Reactive Protein, ESR, Total Leukocyte Count), Renal function test (Creatinine Clearance, Serum Urea, Serum creatinine, serum albumin), Serum electrolytes (sodium, potassium), platelet aggregation and UKPDS risk scoring. hsCRP being an independent predictor of cardiovascular risk, has been considered as primary outcome of this study.

The blood samples were drawn at baseline (first visit) and after 8 weeks (second visit). Biochemical tests were done by Synchron CX systems automated analyzer, and creatinine clearance was calculated by Cockcroft-Gault formulae.^[15] hsCRP was measured quantitatively by solid phase enzyme linked immunosorbent assay (ELISA) using UBI

MAGIWELTM Human CRP ELISA kit. For Platelet Aggregation study, Born's turbidimetric method was followed. UKPDS risk scoring for 10-year risk of Coronary Heart Disease was calculated by the software UKPDS risk engine version 2.

Statistical analysis

The statistical calculations for the paired *t* test and unpaired *t* test were done by statistical software Instat + version 3.036 (Statistical Services Centre, University of Reading, UK). Interval data have been expressed as mean ± SD and categorical data in percentage. Considering hsCRP as primary outcome, sample size has been calculated taking level of significance ($\alpha = 0.05$), power of the study $(1-\beta) = 0.80$ and expected mean difference 0.25. A 'P value' of <0.05 was considered statistically significant. The statistician was blinded to the groups during analysis.

RESULTS

Patient disposition and baseline demographics

A total of 80 patients were randomized to

2 groups to receive either clopidogrel ($n = 40$) or low-dose aspirin ($n = 40$). Post-baseline values were missing in 9 patients (3 in clopidogrel group and 6 in aspirin group) because they were lost to follow-up due to non-compliance. The treatment groups were comparable in demographic features and baseline clinical characteristics [Table 1]. The study population comprised 70% male (56 patients out of total 80 recruited in the study). The mean age of the patients was 64 years in clopidogrel group and 63 years in aspirin group. The patients were suffering from type 2 diabetes mellitus for mean 8.2 years. Anthropometric study reveals that 52.5% patients were overweight (Classification of Obesity, WHO, 1997).^[16]

Efficacy analysis

Change in blood pressure

The decrease in systolic blood pressure were found to be 3.3% ($P = 0.0004$) in clopidogrel group in comparison to 3.3% ($P = 0.005$) in aspirin group. The change in diastolic blood pressure was found to be not significant in aspirin group (1.1%; $P = 0.15$) but in clopidogrel group it was statistically significant ($P = 0.009$). The percentage change in clopidogrel group was compared with that of aspirin group by *t* test and found to be non-significant [Table 2].

Change in metabolic parameters

- Change in glycemic control

In clopidogrel group decrease in fasting blood sugar was significant (4.8%; $P = 0.0001$)

Table 1: Baseline demographic data and clinical characteristics of 80 patients who participated in the study

Characteristics	Clopidogrel group	Aspirin group	P value
Number of patients recruited	40	40	
Number of patients followed-up	37	34	
Male (Sex) (%)	30 (75)	26 (65)	0.46
Age (years)	64.2±5.9	63.2±5.2	0.45
BMI (kg/m ²)	24.8±3.0	25.8±3.7	0.20
Duration of diabetes (years)	7.9±5.3	8.5±5.7	0.65
Number of patients with H/O coronary artery disease (%)	13 (32.5)	09 (22.5)	0.45
Systolic blood pressure (mm of Hg)	138.8±8.5	137.7±9.9	0.59
Diastolic blood pressure (mm of Hg)	86.9±8.0	87.3±5.3	0.83
Fasting blood sugar (mg/dl)	134.15±8.1	132.65±4.6	0.31
Postprandial blood sugar (mg/dl)	232.4±25.8	228.2±23.8	0.45
Glycosylated hemoglobin (HbA1c%)	8.3±1.3	7.9±1.8	0.32
Total cholesterol (mg/dl)	184.1±38.2	194.5±33.1	0.19
LDL cholesterol (mg/dl)	121.1±28.1	126.3±32.8	0.45
HDL cholesterol (mg/dl)	37.6±5.1	38.9±4.1	0.23
Triglyceride (mg/dl)	156.3±66.5	148.5±59.7	0.59
hs C-reactive protein (mg/dl)	1.95±0.85	1.76±0.82	0.29
Total leukocyte count (per cu.mm of blood)	9881±2619	9706±2757	0.77
ESR (mm in 1st hr.)	72.9±29.5	68.6±27.2	0.49
Serum albumin (g/dl)	4.10±0.7	4.01±0.9	0.59
Hb (g%)	11.3±1.7	10.8±1.9	0.25
Creatinine clearance (ml/min)	28.6±10.7	32.0±10.6	0.16
Serum urea (mg/dl)	59.1±23.5	56.6±22.8	0.64
Serum creatinine (mg/dl)	3.2±0.8	3.0±1.0	0.33
Serum sodium (mEq/L)	151.2±7.0	148.7±6.5	0.10
Serum potassium (mEq/L)	4.6±0.7	4.8±0.5	0.19
Serum chloride (mEq/L)	111.9±7.8	109.6±6.1	0.15
Platelet aggregation (in NTU)	187.4±20.3	185.2±13.7	0.54
UKPDS risk scoring (10-year CHD risk in %)	31.6±15.4	28.7±13.2	0.38

Data in mean±SD, BMI=Body mass index, LDL=Low-density lipoprotein, HDL=High density lipoprotein, Hb=Hemoglobin, ESR=Erythrocyte Sedimentation Rate, UKPDS=United Kingdom Prospective Diabetes Study, NTU=Nephelometric Turbidity Unit, CHD=Coronary Heart Disease

Table 2: Changes in different parameters in both the study groups over 8 weeks in follow-up patients

Variables	Clopidogrel group (n=37)			Aspirin group (n=34)			P value [Δ% Clopidogrel group vs. Δ% Aspirin group]	
	1 st visit	2 nd visit	Δ%	P value	1 st visit	2 nd visit		Δ%
Systolic blood pressure (mm of Hg)	139.6±8.2	134.4±4.7	3.7	0.0004*	139.7±9.4	135.1±6.1	3.3	0.005*
Diastolic blood pressure (mm of Hg)	87.1±8.3	83.7±5.2	3.9	0.009*	87.8±5.1	86.8±4.6	1.1	0.15
Fasting blood sugar (mg/dl)	134.9±7.3	128.4±9.3	4.8	0.0001*	131.7±4.7	129.1±8.9	1.9	0.09
Postprandial blood sugar (mg/dl)	231.9±26.6	214.9±25.2	7.3	0.0002*	230.9±24.1	224.4±23.0	2.8	0.002*
HbA1c %	8.25±1.3	8.08±1.2	0.17	0.003*	7.63±1.7	7.56±1.6	0.07	0.07
Total cholesterol (mg/dl)	183.6±39.3	177.8±39.3	3.2	0.02*	192.4±32.5	187.3±31.3	2.7	0.04*
LDL cholesterol (mg/dl)	119.9±28.9	112.8±28.2	5.9	0.0006*	124.5±34.8	124.8±30.2	-0.24	0.92
HDL cholesterol (mg/dl)	37.9±5.1	38.3±3.8	-1.1	0.45	39.3±4.2	38.1±2.2	3.1	0.04*
Triglyceride (mg/dl)	153.5±68.2	140.8±52.8	8.3	0.0001*	150.9±63.7	145.2±51.9	3.8	0.07
hs C-reactive protein (mg/dl)	2.0±0.9	1.83±0.7	8.5	0.0002*	1.72±0.8	1.69±0.6	1.7	0.74
Total leukocyte count (per cu.mm of blood)	9853±3076	8838±2129	10.3	0.02*	9702±2987	9412±1984	2.9	0.25
ESR (mm in 1 st hr.)	72.1±28.4	66.8±25.2	7.4	0.006*	73.3±28.4	69.5±24.6	5.2	0.04*
Creatinine clearance (ml/min)	28.1±10.9	30.4±8.2	-8.2	0.0009*	32.4±10.9	31.6±8.8	2.5	0.18
Serum urea (mg/dl)	59.9±23.7	55.8±22.9	6.8	0.01*	58.1±23.4	57.5±17.1	1.0	0.77
Serum creatinine (mg/dl)	3.1±0.9	2.7±0.7	12.9	0.0001*	3.3±0.8	3.1±0.6	6.0	0.09
Serum albumin (g/dl)	4.08±0.7	4.45±0.5	-9.2	0.0001*	4.02±0.9	4.10±0.7	-1.9	0.25
Serum sodium (mEq/L)	151.5±7.0	146.1±6.3	3.6	0.0002*	148.6±6.2	147.1±4.9	1.0	0.07
Serum potassium (mEq/L)	4.61±0.7	4.41±0.5	4.3	0.003*	4.72±0.5	4.60±0.3	2.5	0.06
Platelet aggregation (in NTU)	187.4±21.1	139.7±25.2	25.5	<0.00001*	184.1±12.9	125.6±14.1	31.2	<0.00001*
UKPDS risk scoring (10-year CHD risk in %)	30.1±14.8	27.7±13.1	7.9	0.006*	27.4±13.6	26.9±13.7	1.8	0.36

Data in mean±SD. Δ% Percentage change over 8 weeks., LDL=Low-density lipoprotein, HDL=High density lipoprotein, Hb=Hemoglobin, ESR=Erythrocyte Sedimentation Rate, UKPDS=United Kingdom Prospective Diabetes Study, NTU=Nephelometric Turbidity Unit, CHD=Coronary Heart Disease, *Statistically significant

but the change in aspirin group was 1.9%, which was not significant. The change in postprandial blood sugar in both the groups were significant and when the percentage changes in individual group were compared, the change in clopidogrel group was found to be significant over aspirin group ($P = 0.03$). The control of glycosylated hemoglobin was found to be better in clopidogrel group where the decrease in HbA_{1c} was statistically significant ($P = 0.003$) but the change in aspirin group was insignificant ($P = 0.07$) [Table 2].

- **Change in lipid profile**

There was decrease in total cholesterol by 3.2% in clopidogrel group in comparison to 2.7% in aspirin group. The changes in individual groups were significant but the comparison between the percent changes in the groups was not found to be statistically significant. LDL cholesterol was decreased by 5.9% ($P = 0.0006$) in clopidogrel group whereas in aspirin group there was an increase by 0.24%. The percent change in clopidogrel group was found to be significant ($P = 0.02$) over aspirin group. In clopidogrel group there was an increase of HDL cholesterol by 1.1% in comparison to a 3.3% decrease in aspirin group. There was 8.3% ($P = 0.0001$) decrease in serum triglyceride in clopidogrel group, whereas in aspirin group the change was 3.8%, which was not significant [Table 2].

Change in renal function

There was a decrease in serum urea level by 6.8% ($P = 0.01$) in clopidogrel group, whereas for aspirin group it was 1%. The changes of the individual group were tested for significance and the percentage change in clopidogrel group was found to be highly significant ($P = 0.008$) over aspirin group. Clopidogrel group experienced a decrease of 12.9% ($P = 0.0001$) in serum creatinine as compared to 6% in aspirin group. The change in clopidogrel group was found to be statistically significant ($P = 0.02$) over aspirin group by *t* test. In clopidogrel group there was an increase in creatinine clearance by 8.2% ($P = 0.0009$) but in aspirin group it was decreased by 2.5%. The change in clopidogrel group was found to be highly significant ($P = 0.0008$) over aspirin group. In clopidogrel group there was an increase of serum albumin by 9.2% in comparison to 1.9% in aspirin

group. The percentage change in clopidogrel was found to be significant ($P = 0.02$) when compared to the change in aspirin group [Table 2].

Change in electrolytes

In both the study groups there were borderline hypernatremia. After 8 weeks, there was a decrease of 3.6% ($P = 0.0002$) in serum sodium in clopidogrel group as compared to only 1% decrease in aspirin group. The percent change in clopidogrel group was found to be statistically significant ($P = 0.02$). In both groups mean serum potassium was at a high normal level. In clopidogrel group there was a decrease of 4.3% ($P = 0.003$) in serum potassium, which was statistically significant but in aspirin group the change (2.5%) was not significant [Table 2].

Change in inflammatory biomarkers

hsCRP was found to be decreased significantly by 8.5% ($P = 0.0002$) in clopidogrel group in comparison to 1.7% in aspirin group. The change in clopidogrel group was not found to be significant over aspirin group. The changes in ESR were 7.2% and 5.2%, respectively in clopidogrel and aspirin group. Though individually the changes were significant, the change in clopidogrel was not significant over aspirin group. A decrease of 10.3% in TLC was found in clopidogrel group whereas it was only 2.9% in aspirin group. The change in clopidogrel group was not statistically significant over aspirin group [Table 2].

Change in platelet aggregation

The change in platelet aggregation was found to be significant in both groups. In aspirin group there was a decrease of 31.2%, whereas it was 25.5% in clopidogrel group. The change in aspirin group was found to be statistically significant over clopidogrel group [Table 2].

Change in UKPDS risk scoring

A 10-year risk of CHD was found to decrease significantly (7.9%; $P = 0.006$) in clopidogrel group, whereas 1.8% decrease in aspirin group was insignificant [Table 2].

DISCUSSION

The control of both systolic and diastolic blood pressure was found to be better controlled with clopidogrel group than aspirin group and it is a clear advantage of using clopidogrel in patients of CKD with type 2 diabetes mellitus where

hypertension can lead to added complications. There is improvement in glycemic status in both the groups but both fasting and postprandial blood glucose was decreased more in clopidogrel group. As the study population was suffering from diabetes for an average of 8 years, the long-term glycemic status was important and measured by glycosylated hemoglobin. It is known that glycosylated hemoglobin concentration predicts cardiovascular risk both in diabetic and non-diabetic population, and may help identify individuals at higher risk of cardiovascular disease for targeted interventions, including blood pressure or cholesterol reduction.^[17-19] So by better controlling HbA_{1c} level, clopidogrel has established its better cardioprotective role when compared to low-dose aspirin. In lipid profile, a significant improvement in serum triglyceride, total cholesterol and LDL cholesterol level in clopidogrel group can directly help in retarding the process of atherosclerosis and development of (CAD) Coronary Artery Disease.

As the study population was suffering from chronic renal disease, assessment of renal function was done by serum urea, creatinine, creatinine clearance and serum albumin. There was significant improvement in all the renal parameters in clopidogrel group but in aspirin group creatinine clearance was decreased suggesting a re-evaluation of the status of low dose aspirin as add-on therapy in chronic renal failure. The previous study by Refael Segal *et al.*, concluded that short-term low-dose aspirin affected renal tubular creatinine and uric acid transport in the elderly, which may result in a prolonged or permanent deterioration of the renal function.^[16] In our study groups, we found hypernatremia and high than normal potassium level. After 8 weeks follow-up electrolyte status has been improved in both groups but clopidogrel group has shown a promising decrease in serum sodium and potassium level.

C-reactive protein is a reliable marker of cardiovascular risk and its therapeutic implications in end-stage renal disease patients has been shown by Park *et al.* in 2003.^[20] Renal insufficiency has been found to be independently associated with elevations in inflammatory biomarkers.^[21] The robust association with future cardiovascular events has provided an analytic opportunity for CRP in clinical use. Based on multiple epidemiological and intervention studies, minor CRP elevation

has been shown to be associated with future major cardiovascular risk (hsCRP: <1 mg/L = low risk; 1-3 mg/L = intermediate risk; 3-10 mg/L = high risk; >10 mg/L = non-specific elevation).^[22] Total 76% patients (61/80) of our study population were found to have intermediate risk, whereas rest of the patients had low risk for cardiovascular diseases. In our study along with hsCRP, we have also estimated 2 supporting non-specific inflammatory marker ESR and TLC. All the 3 inflammatory biomarkers were found to be decreased significantly in clopidogrel group promising a significant reduction in cardiovascular morbidity and mortality. Though 8 weeks is relatively short time to assess cardiovascular risk, these findings clearly establishes superior cardioprotective role of clopidogrel.

Platelet activation is involved in the pathogenesis of chronic renal injury. Intrarenal platelet activation is an important component that contributes to glomerular sclerosis and interstitial fibrosis. Some studies showed that platelet activation is closely related to inflammation, and platelet activation can induce or increase inflammation in vivo. So inhibition of the platelet activation contributes to the repression of the inflammation. The platelet aggregation study shows that both the anti platelet drugs were significantly decreased platelet aggregation. Though anti-aggregatory effect was more with aspirin, the effect of clopidogrel was found to be considerably close to low dose aspirin.

The UKPDS risk engine is the first coronary risk calculator to be developed from a cohort with type 2 diabetes. It showed good predictive ability and the risk engine has been externally validated using data from the CARDS study.^[17,23,24] Finally UKPDS scoring for 10-year risk of CHD shows a significant decrease in clopidogrel group when compared with aspirin group. This improvement is an overall improvement in lipid profile, glycemic control, control of blood pressure and inflammatory status in clopidogrel group.

Recent understanding of pathogenesis of chronic renal disease may explain superiority of clopidogrel found in this study. Diffuse glomerular sclerosis and interstitial fibrosis contribute to the progression of renal damage and constitute the final common pathway for almost all forms of kidney diseases.^[18] In recent years, more attention has been focused on the inflammatory infiltration present in various

types of progressive renal diseases in humans and in experimental models. The number of inflammatory cells in the renal tissue closely correlates with the severity of glomerular and tubulointerstitial lesions and loss of renal function. Inflammatory cells and activated intrinsic kidney cells can produce various cytokines, which can promote the progress of glomerular sclerosis and interstitial fibrosis, so it may be a novel therapy strategy for chronic renal disease to reduce the infiltration of inflammatory cells.^[19] Mounting evidence has shown that platelet activation and angiotensin II can promote glomerular inflammation and fibrosis and play a pivotal role in the progression of CKD.^[25-27] A variety of cytokines, including TGF- β_1 and CTGF (connective tissue growth factor) are important for renal cell proliferation and extracellular matrix production.^[28-30] Clopidogrel therapy has been found to almost completely abolish macrophage infiltration and attenuated the expression of monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1, TGF- β_1 and CTGF.^[31] So superiority of clopidogrel found in this study may be attributed to its additional anti-inflammatory effect established by Xiaowen Tu *et al.*

CONCLUSIONS

The salient benefits of clopidogrel over aspirin given as prophylactic therapy against coronary events in patients with chronic renal failure with type 2 diabetes has been assessed in our study. The better control of metabolic parameters, renal function and inflammatory burden was evident in clopidogrel group and a significant decrease in 10-year risk of CHD has proved its superiority over low-dose aspirin in chronic renal failure. This study renders support to future prospective clinical studies of clopidogrel in chronic kidney disease and its sequels. Because non-blinding and single center were limitations, the findings of this pilot study should be confirmed by multicentric, randomized, double-blind, large population studies.

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