

# Impact of lipid disorders on mortality among Saudi patients with heart failure



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**Background:** Dyslipidemia, a known cardiovascular risk factor, is extremely common among Saudis, both adults and children. The impact, however, of dyslipidemia and several other lipid disorders in patients with congestive heart failure in this particular population has not been documented. This study aims to fill the gap.

**Methods:** This retrospective, single center study was conducted at King Abdulaziz Medical City, Riyadh, Saudi Arabia. Of the 500 cases seen during the period between 2002 and 2008, 392 were included in the study. Charts were reviewed and information on medical history, medications, and lipid status were documented.

**Results:** Low HDL-cholesterol level was the most common lipid disorder with 82.9%, followed by hypertriglyceridemia (35.2%), atherogenic dyslipidemia (27.8%), and hypercholesterolemia (9.2%). Diabetes mellitus was the single most significant predictor of mortality ( $p = 0.001$ ). Among the lipid disorders, only low levels of HDL-cholesterol contributed to significant mortality risk [OR 1.29 (Confidence Interval 1.04–1.59) ( $p$ -value < 0.01)] adjusted for age, gender and statin use.

**Conclusion:** The results of this study suggest that emphasis should be on the elevation of HDL-cholesterol levels among subjects with congestive heart failure, without compromising any ongoing management of LDL-lowering drugs. Management should not be limited to conventional statin use and should promote other treatments to elevate HDL-cholesterol levels.

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**Keywords:** Congestive heart failure, Lipid disorders, Saudi Arabia

## Background

Lipid disorders are considered major risk factors for vascular diseases including coronary heart diseases that account for the majority of

over-all cause mortality [1]. Furthermore, dyslipidemia, defined as having abnormal levels of circulating lipids, is common even among apparently healthy individuals with no manifestations of cardiovascular disease [2]. While studies conducted

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in the Kingdom of Saudi Arabia (KSA) with regards to dyslipidemia have only recently begun to flourish, recent epidemiologic data reveal that dyslipidemia is the most common cardiovascular risk factor in both children [3] and adults [4], with an estimated nine out of every 10 Saudis having low levels of HDL-cholesterol. Despite these staggering figures, however, the country has a relatively low prevalence of coronary heart disease (age-adjusted prevalence of 6.9%) as compared to other developed nations, and this is primarily due to the relatively young population in the kingdom [5]. Nevertheless, having the predisposition to develop dyslipidemia, or any other cardiovascular risk factors at an early age, may potentially overwhelm the public health sector in the long run if no aggressive interventions are carried out. In fact, regional information, though scarce, already reveals that people from Africa and the Middle East present with myocardial infarction at a relatively younger age when compared to other ethnicities, and deaths attributed to coronary artery diseases are projected to increase at an overwhelming rate of 171% between 1990 and 2020 [6].

In the present single-center retrospective study, and for the first time in the Saudi Arabian population, we sought to determine which among the commonly encountered lipid disorders (low HDL-cholesterol, hypertriglyceridemia, hypercholesterolemia and atherogenic dyslipidemia) predispose patients with established heart failure (HF) to increased mortality. We also assessed the prevalence of the various lipid disorders among this population group.

## Materials and methods

This single-center, retrospective study was conducted at King Abdulaziz Medical City (KAMC), Riyadh, KSA. The charts of 500 patients, admitted secondary to HF [defined as systolic heart failure or HF with reduced ejection fraction (EF)  $\leq$ 40%] and/or HF with preserved EF (EF  $\geq$  50), [7] who were diagnosed either clinically and/or by echocardiogram and/or cardiac catheterization], or who visited the out-patient department for the same complaint between the years 2002 and 2008 were reviewed and screened for inclusion. Cases were excluded if the HF was congenital in origin, end-stage renal disease (ESRD), or if the patient was above 90 years of age. From the roster of cases, a total of 392 cases met the criteria for this study. Information gathered included demographics, medical history, and medications taken.

### Abbreviations

HF	heart failure
DMT2	diabetes mellitus type 2

Laboratory results obtained during admission/evaluation were also obtained and included lipid profiles. For the purpose of this study, atherogenic dyslipidemia was defined as triglycerides  $>$ 1.69 mmol/l and either HDL  $<$ 1.03 mmol/l (men) or HDL  $<$ 1.29 mmol/l (women) [8]. Hypercholesterolemia was defined as serum total cholesterol concentration  $\geq$ 5.18 mmol/l [9].

### Data analysis

Raw data were encoded in MS Excel spreadsheet. Data were analyzed using the Statistical Package for the Social Sciences version 17.0 (SPSS, Chicago, IL, USA). Frequencies were presented as percentage (%). Odds ratio was obtained to determine mortality risk among lipid disorders. Multinomial logistic regression analysis was performed using mortality as dependent variable and all the categorical variables (medications as confounders) measured as independent variables to determine which among the diseases of interest had the most significant impact in predicting mortality in the cohort. Significance was set at  $p < 0.05$ .

## Results

Table 1 highlights the demographic characteristics of the subjects. More than half of the subjects included were men (53.1%) and the over-all mortality was 52.3%. No significant difference was observed between the mortality of males versus females ( $p = 0.56$ ). Among the diseases listed,

Table 1. General characteristics of patients.

N	392
Males	208 (53.1)
Age (years)#	67.77 (12.8)
Mortality	205 (52.3)
Hypertension	333 (84.9)
Low HDL-cholesterol	325 (82.9)
Hypertriglyceridemia	138 (35.2)
Hypercholesterolemia	36 (9.2)
Atherogenic dyslipidemia	109 (27.8)
Smokers	60 (15.3)
Diabetes mellitus type 2 (DMT2)	242 (61.7)
Valvular disease	45 (11.5)
Ischemic cardiomyopathy	268 (68.5)
Chronic atrial fibrillation	103 (26.3)
PTCA/CABG	91 (23.2)
Stroke/TIA	89 (22.7)

Note: Data presented as N (%); # denotes mean (standard deviation).

Table 2. Medications of subjects.

Medications	
ACE I	175 (45.1)
ARB	135 (34.8)
β-Blockers	269 (69.3)
Diuretics	298 (76.8)
Spirolactone	88 (22.7)
Statins	273 (70.7)
Nitrates	52 (17.7)
Anti-arrhythmic	22 (5.7)
Digitalis	55 (14.2)
Aspirin	241 (62.3)
Warfarin	70 (18.1)
Plavix	85 (22.0)
CRT, ICD, combined	35 (9.0)

Note: Data presented as N (%).

hypertension was noted to be the most common (84.9%) followed by ischemic cardiomyopathy (68.5%) and DMT2 (61.7%). Among the lipid disorders, low HDL-cholesterol level was the most common lipid disorder with 82.9%, followed by hypertriglyceridemia (35.2%), atherogenic dyslipidemia (27.8%) and hypercholesterolemia (9.2%). Table 2 shows the medications used by the subject. Worthy of note is that 70% of the subjects were on statin treatment. Table 3 shows the odds ratio for the different diseases present in the cohort in relation to mortality while adjusting for age, gender, and medication use, and revealed that diabetes mellitus is the single most significant predictor for mortality ( $p = 0.001$ ). Also worthy of note, though not significant probably due to sample size, was low HDL-cholesterol which falls second to DMT2 in terms of mortality risk ( $p = 0.11$ ). Fig. 1 reveals that among the four lipid disorders described in the present study, only low levels of HDL-cholesterol contributed to significant mortality risk [OR 1.29 (Confidence Interval 1.04–1.59)] ( $p$ -value < 0.01) adjusted for age, gender, and statin use.

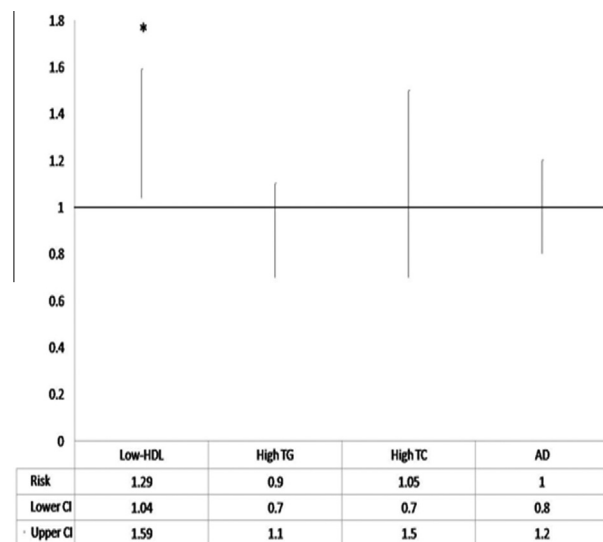


Figure 1. Low levels of HDL-cholesterol contributed to significant mortality risk.

## Discussion

The main findings in this study reveal that the prevalence of lipid disorders remains high, particularly low HDL-cholesterol levels, despite the majority of subjects taking lipid-lowering agents, and that DMT2 is the significant independent predictor of mortality among Saudi patients with congestive heart failure. The presence of DMT2, which on its own is considered a vascular disease, is a major cardiovascular risk factor and is expected to remain significant even after adjustment for all documented confounders. Notably, more than 60% of the patients included harbor DMT2, although hypertension was more common. Furthermore, it has been well established from population-based studies that decreased levels of HDL-cholesterol are associated with increased risk of cardiovascular morbidity and mortality [10–14]. While the present study confirms a

Table 3. Multi-logistic regression analysis using mortality as dependent variable.

Variables measured	Coefficient β	Odds ratio	95% CI	P-value
Hypertension	0.80	1.08	0.69–2.0	0.79
Ischemia	0.001	1.00	0.61–1.66	0.99
PTC/CABG	–0.22	0.79	0.47–1.35	0.40
Stroke	0.12	1.12	0.66–1.92	0.37
Diabetes mellitus	–0.76	0.47	0.30–0.75	0.001
Hypercholesterolemia	–0.16	0.85	0.39–1.86	0.69
Low HDL-cholesterol	–0.63	0.53	0.25–1.14	0.11
Hypertriglyceridemia	0.16	1.17	0.39–3.52	0.78
Dyslipidemia	–0.146	0.86	0.26–2.82	0.81

Note: Results were adjusted for gender and all the medications listed in Table 2. Significant at  $p < 0.05$ .

plethora of scientific evidence with regards to HDL-cholesterol and mortality, it also illustrates that a very high incidence of dyslipidemia, particularly low HDL-cholesterol, persists even among patients already taking lipid-lowering medication. As previously mentioned, epidemiologic evidence already points to increased incidence of low HDL-cholesterol even in an apparently healthy population [3,4], and this incidence remains true for the population used in this study. The majority of the study subjects were on statins, and while the major effect of the drug is on total cholesterol, it exerts a minor yet significant effect in elevating HDL-cholesterol levels, aside from its conventional role of decreasing over-all circulating cholesterol levels [15]. It was expected, therefore, that the incidence of this type of lipid disorder would be lower, yet the result was the same when compared to the general population.

A low HDL-cholesterol level is one of the criteria for metabolic syndrome. It has major vasoprotective and anti-inflammatory effects, while low concentrations of HDL-cholesterol have been associated with the development of atherosclerosis, CVD, and decreased life expectancy [16]. Low HDL-cholesterol is highly heritable in Saudi families and begins to manifest as early as the pre-teenage years [17]. Epidemiological studies show there is a geographic prevalence gradient with the lowest levels in Saudi Arabia, intermediate levels in Asia Minor, and highest levels in western Europe [18,19]. While information on the reasons for the prevalence of depressed levels of HDL cholesterol in the Saudi population is scarce, several local interventional studies point to improvement in circulating HDL-levels and other cardiometabolic parameters after vitamin D correction. Although vitamin D levels were not assessed in the present study, it is interesting to note that vitamin D deficiency is equally prevalent in KSA [20–21]. The equally low levels of vitamin D in the Saudi population may offer insights on how to address the low levels of HDL-cholesterol, aside from the use of conventional drugs.

The results of the present study have clinical implications. First, clinical management should include elevating/normalizing HDL-cholesterol levels among subjects with HF, without compromising existing management of LDL-lowering drugs. There is a need to study HDL-cholesterol in-depth in this particular population, as the incidence of low HDL-cholesterol is not limited to adults but is extremely high, even among children. Furthermore, the consideration of ethnic differences with a more tailored approach in

treating Saudi patients with HF is an essential undertaking.

The study has several limitations. Present findings may not apply to other populations, as all the subjects of the present study have HF. Furthermore, the small sample size and the single-center approach limit the findings of the study and therefore cannot be generalized as applicable to all patients with congestive heart failure unless done on a larger scale. Nevertheless, this is the first study to document the persistence of the extremely high prevalence of low HDL-cholesterol among Saudi patients with HF and on statins, as well as the significant impact of DMT2 in contributing to the over-all mortality rate of this population. Management should not be limited to conventional statin use and should promote other treatments and non-pharmacological options, such as vitamin D correction, that might potentially elevate HDL-cholesterol levels.

## Disclosures

None.

## Ethical consideration

The study was reviewed by the prospective research committee.

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