THE UTILITY OF MOBILE PHONE IN THE PREVENTION OF CORONARY HEART DISEASE, THROUGH LIFESTYLE MODIFICATION: A PROSPECTIVE, RANDOMIZED, CONTROLLED CLINICAL TRIAL.

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This thesis is presented for the degree of Doctor of Philosophy in

Advanced Medicine – PhD (Advanced Medicine).

DEDICATION

Dedicated to my family, for their support and encouragement, which led me to this endeavor.

and also,

Dedicated to all of my study participants who shared their experiences for the benefit of others

THE UTILITY OF MOBILE PHONE IN THE PREVENTION OF CORONARY HEART DISEASE, THROUGH LIFESTYLE MODIFICATION: A PROSPECTIVE, RANDOMIZED, CONTROLLED CLINICAL TRIAL.

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ABSTRACT

Background:

Unhealthy diet, cigarette smoking, pollution, sedentary lifestyle, and psychological factors such as depression and anxiety are among the major modifiable risk factors for coronary artery disease (CAD). Mobile phone text messaging (SMS) holds promise as an affordable, effective and far reaching means to effect behavioral changes in health education, and health care management.

Objective:

This randomized clinical trial explored the effectiveness of a SMS intervention program for improving major risk factors among (CAD) patients and their care-givers.

Methodology:

This randomized clinical trial was conducted in 3 cardiac specific tertiary care hospitals in Karachi, Pakistan. Participants were patients who had their first cardiac events and their respective nominated care-givers. Patients and their care-givers were randomized into two groups, intervention (IG) or usual care group with no-intervention (NIG). For the participants in the IG, daily 5 days per week, health text messages were sent to their mobile phones. Patients and their care-givers in both groups were followed up at 3 monthly intervals.

Results:

A total of 2656 patients and 559 care-givers were recruited. Minimum follow-up period was 180 days (range: 180 to 400 days). Baseline characteristics of participants in intervention and non-intervention group were similar in patients and caregivers. Analysis revealed that motivational psychological wellbeing SMS messages through mobile phone does not have any significant effect in promoting psychological wellbeing. There were 41 deaths in intervention and 45 deaths in non-intervention groups (total 86). The mean survival time (534 days) in

intervention group and mean survival time (514 days) in non-intervention was not significantly different.

Conclusions:

A novel approach was adopted by recruiting caregivers as a parallel group along with their respective CAD patients. SMS text messaging alone was not effective in improving the psychological wellbeing of our study participants. Future studies with such populations may explore augmenting SMS with brief face-to-face counselling sessions. Probably, any intervention to prevent CAD will not be successful, unless there is a conducive environment provided by the government to adopt and afford the healthy lifestyle by every section of society in Pakistan.

Key words: coronary artery diseases, caregivers, text messages, intervention, diet, physical activity, psychological stresses, clinical trial

Note: *mobile phone text messages and SMS were used interchangeably in this thesis*

Statement of Candidate

I certify that the work in this thesis entitled "Mobile phone-text messages assisted lifestyle modifications for the prevention of coronary heart disease among coronary artery disease patients and their caregivers: – A randomized clinical trial, Pakistan" has not previously been submitted as part of requirements for a degree to any other university or institution other than Macquarie university

I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis.

The research presented in this thesis was approved by Macquarie University Ethics Review Committee, reference number: 5201100109. The research presented is also registered at Australia-New Zealand clinical trial registration, ANZCTR Reg. No: ACTRN12611000388910.

Signature
Javed Ismail (Student ID: 41944852)

Date

Acknowledgements

I wish to thank my supervisors Professor Hosen Kiat, Dr. Esben Strodl, Dr. Junaid Ansari and Dr. Jun Ma for their guidance, valuable advice and continuous support. I have gained a wealth of knowledge by their invaluable experience, wisdom and constant encouragement. You have taught me so much; I cannot thank you enough.

I am grateful to the Macquarie University for the scholarship, which enabled me to complete this study.

A special note of thanks to my wife Farah for her continuous support, and sharing extra burden during this endeavor, to my lovely daughters, Maryum, Fatimah, and Zainab for being so loving and understanding, and to my late mother (Hayat Begum), who always been to me like a North star, which guides me to reach my destination.

I wish to thank Cardiac Health Institute, Sydney for their financial support, and Dr. Essa laboratories, Pakistan, in subsidizing the laboratory investigation for our study. To all the collaborating sites in Karachi (National Institute of Cardiovascular Diseases, Karachi Institute of Heart Diseases, Tabba Heart Institute) for their permission and support to collaborate in our study.

This acknowledgment will be incomplete without offering my heartfelt thanks to my data collectors, Ms. Mehreen, Ms. Javeria, Ms. Yusra, Ms. Safia, Ms. Sauleha, and Ms. Sobia, for their dedication, hard work and bearing with me the period of financial hardship. Thank you for accompanying me in a roller coaster like experience during the data collection.

My deepest thanks must go to my study participants who gave their time so generously and shared their experiences for the benefit of others. I am honored to share your experiences, Thank you

THANK YOU ALL, and TO THOSE WHO HAVE PRAYED FOR MY SUCCESS

CHAPTER 1:

INTRODUCTION

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TITLE:

Mobile phone-assisted lifestyle modifications to prevent coronary heart disease – randomized controlled clinical trial.

INTRODUCTION:

Thirty-one percent (17.5 million) of all global deaths in 2012 were due to CVD and among CVD deaths, 7.4 million deaths were due to coronary artery disease (CAD) [1, 2]. While CAD is the single largest cause of death in developed countries, it is also one of the leading causes of death in developing countries [1-3]. Three-quarters of global deaths due to CAD (nearly 80%) occurred in low and middle-income countries, the majority of, which were considered premature deaths (under the age of 70 years) [1-5]. South Asians (India, Pakistan, Bangladesh, and Sri Lanka) comprises 25% of the world's population and suffers from nearly 60% of the global CVD burden [6-8]. Global burden of disease (GBD) 2010 reported that South Asian countries had the high CAD burden, and more than 29% of men and 24% of women who suffered CAD were < 50 years-old [9]. CAD in South Asians occurs at a younger age, is more aggressive, and has a higher overall mortality [10-12]. The South Asia region had the highest number of life-year lost to premature CAD [13]. Premature CAD deaths indicate that it is more likely to occur in productive, working-age adults, which represents the greatest loss for families and national economics [14]. The age of onset of first CAD among SA population, on an average, is 10 years earlier compared with other populations, and this is largely attributable to higher prevalence of CAD risk factors at younger ages [15]. Studies among SA migrant have found that the mortality rate attributable to CAD among SA younger than 30 years is 3 fold higher than for Caucasians in the United Kingdom and 10-fold higher than the Chinese in

Singapore [16, 17]. It has been reported that the likelihood of developing CAD in South Asians is about 2 time higher than in European and 5 time higher than Chinese [6, 18, 19]. In 2005, the estimated mortality associated with CVD was 29% in India [20]. Pakistan with more than 185 million people is the sixth most populous country in the world. Data from Pakistan in the GBD 2010 study showed that CVD was responsible for 18% of crude deaths and 26% of age standardized deaths, making them the leading cause of deaths in individuals within a productive age group of 30 – 69 years [21]. It has been suggested that one in four middle-aged adults in Pakistan has prevalent CAD [25]. The projected crude yearly mortality per 100000 populations in Pakistan from 2010 to 2025 for CVD was reported to increase from 125.5 in 2010 to 144.4 in 2025 [22]. The cumulative deaths from CVD, cancers and chronic respiratory diseases in people aged 30 – 69 from 2010 to 2025, in Pakistan is predicted to be 3.87 million [22].

A large epidemiological case-control study, INTERHEART, suggest that 90% of the attributable risk for CAD can be explained by 9 risk factors, which belongs to behavioral and physiological groups. The 9 risk factors are 1) low consumption of fruits and vegetables 2) tobacco smoking; 3) alcohol consumption; 4) psychosocial factors; 5) sedentary lifestyle; 6) hypertension; 7) dyslipidemia; 8) abdominal obesity; and 9) diabetes [23]. Previous studies have reported that the South Asian population which suffered from CAD had an increase prevalence of tobacco smoking, low consumption of fruits and vegetables, decreased physical activity, high level of stress and other psychosocial risk factors, diabetes, hypertension [15, 20, 24-27]. Leading attributable risk factors for death from CVD in Pakistan in 2010 and also projected for 2025, in descending order are, tobacco use, high blood pressure, low intake of fruits and vegetables, suboptimal blood glucose, overweight and obesity, physical inactivity and total cholesterol [28]. GBD 2013 study stated that major risk factors associated with CAD are modifiable indicating a huge potential for prevention [29]. At least 80% of premature deaths from heart disease can be avoided by engaging in regular physical activity, avoiding tobacco

use and second-hand tobacco smoke, choosing a diet rich in fruit and vegetables, avoiding foods that are high in fat, sugar and salt, and maintaining a healthy body weight[30]. A recent study found that 4 out of 5 myocardial infarctions (MIs) in men could be prevented by following a healthy diet, being physical active (walking/bicycling ≥ 40 min/day and exercising ≥ 1 hr./week), moderate alcohol use (10 - 30 g/day), having no abdominal adiposity (waist circumference < 95 cm), and refraining from smoking[31]. In the last couple of decades, a sleuth of studies also identified depression, anxiety and other psychosocial factors, including nonphysical stress as potent risk factors for CVD, associated with an increased risk of mortality [32-36]. Psychosocial risk factors (PSRFs), like depression and anxiety, are not only associated with the incidence of CAD, but it also contributes in low-health related quality of life, recurrent cardiac events, CAD related and all-cause mortality, and poor prognosis in established CAD patients [36, 37]. Being a patient of CAD and having a lifelong treatment increases the level of depression and anxiety, which gradually instill the fear of dying and helplessness [37]. That fear of death and helplessness may negatively affect the prognosis after CAD [37]. Studies done on CAD patients with depression and anxiety showed that presence of depression and anxiety may affect behaviours change such as, smoking, dietary preferences, physical activity, which in turn can influence the risk of CAD [38]. CAD patients with depression tend to have unhealthier diets, smoke more, engage in less physical activity, are less likely to seek medical care, and have poorer adherence to medical regimen [39, 40]. As such mental health conditions such as depression are important targets for intervention in CAD patients.

National Health Survey of Pakistan (NHSP) 1990 – 94 reported that the prevalence of hypertension in adults (≥ 15 years) was 18%, one in four were overweight (BMI > 23kg/m^2), and 90% of the population did not consume the targeted 5 servings of fruits and vegetables [41-43]. Pakistan Diabetes Survey (PDS) showed prevalence of diabetes in adults ≥ 25 years was 22% in urban areas [44]. Prevalence of anxiety and depression in adult population of Pakistan

was reported to be 34% (range 29% – 66% for women and 10% – 33% for men) [45]. In Pakistan only 3% – 6% of hypertensive are under satisfactory control [46, 47]. A systematic analysis of 2013 study stated that in 2013 dietary risks accounting for 11.3 million deaths and 241.4 million disability-adjusted life-years (DALYs), high systolic blood pressure for 10.4 million deaths and 208.1 million DALYs, tobacco smoke for 6.1 million deaths and 143.5 million DALYs, and high body mass index (BMI) for 4.4 million deaths and 134.0 million DALYs [29].

It has been projected that the number of attributable deaths in Pakistan from NCD in 2025 in all adults aged 30 – 69 years can be averted if key risk factors were reduced by the specified level. The projected most substantial reduction in the number of deaths was noted with the reduction of mean systolic blood pressure by 3 mmHg (20700 deaths), whereas 30% reduction in the prevalence of tobacco use could avert 19500 deaths, reduction in fasting blood glucose level by 0.25 mmol/L (11200 deaths) reduction in body mass index by 0.15 kg/m2 (8800 death) increase in physical activity to 50% of recommended level (6500 deaths), and increase in intake of fruits and vegetables by 50 g/day could avert 3000 deaths[22]. Cumulative reduction at specified level by all seven risk factors the specified t 62700 deaths in 2025, and 623900 from 2015 to 2025 [22]. Current health system in Pakistan is unable to manage the increasing burden of NCD, with total per person expenditure of less than a total $ 18 per year, which is lower than neighboring India and Sri Lanka [22]. There is no separate budget allocated for prevention and rehabilitation program for NCD [22]. WHO and Non-communicable disease alliance recommended 25% reduction in overall mortality rate from CVD, cancers diabetes and chronic respiratory diseases in adults aged 30 – 70 years [48]. It has been projected that if an effective intervention could be implemented for the combined reduction in the risk factors of tobacco use, systolic blood pressure , cholesterol, and diabetes, it could avert 730000 deaths from projected 3870000 due to CVD, in individuals aged 30 – 69 years, at different time points in

Pakistan from 2010 to 2025 [22]. Interventions targeting the mentioned risk factors have been referred as the best buys in terms of cost effectiveness and feasibility by WHO cost-effectiveness and feasibility in low and middle income countries. Several reports examined national capacities to implement CVD prevention and treatment program and concluded that in majority of the countries there was little prevention strategies to combat CVD epidemic or will to take action [49, 50].

Literature is replete with research outcomes on patient centered care, but little information is available on patients' informal care givers. Family care giving is defined as extensive care to the patients, without any financial benefits, by spouses, parents, and loved ones[51]. Caregivers are usually involved in direct assistances (e.g., helping in daily activities, medication, and lifestyle management), monitoring symptoms, maintaining physician appointment and accompanying at physician clinic[51]. All these additional workloads put caregiver at "caregiver strain", which causes sleep disturbance, physical exhaustion, change in personal plan, depression, anxiety, financial constraint, and poor self-rated health [52-55]. Family caregivers has an important role and it has been recognized, but high physical, and psychosocial demand expose them at greater risk of ill health, even mortality due to CVD [54, 56]. Intervention has been recommended for the wellbeing of the caregiver[57], but, to our knowledge, none has been developed and implemented.

Changing modifiable risk factors, however, is not straightforward with many primary and secondary preventive strategies failing to achieve their desired goals [58, 59]. The WHO-PREMISE project showed that a significant number of patients fail to adopt healthy lifestyle habits after a major cardiovascular event, 12.5% of the studied patients continue to smoke, 38.4% do not comply with dietary advice, and 52.5% do not engage in regular physical activity [59]. The results of the WHO-PREMISE project underscore the need for novel strategies to improve compliance and persistence in risk factor modification measures. Numerous studies

conducted in UK, and USA reported a general deficit in knowledge concerning CAD, its prevention and health promotion among SA immigrants [60, 61]. In Pakistan, where there is a high and increasing prevalence of CAD, and the majority of the population lacks substantive knowledge on risk reduction related lifestyle modification measures [62, 63]. It is not only that general population's lack knowledge on risk reduction, even health professionals fail to educate their patients. Seventy-five percent of Pakistan's population consult private family physicians for their primary health care, but there are serious deficiencies in family physician's knowledge, management, and prevention of hypertension and CVD [54]. Knowledge on risk reduction related lifestyle modification is the key to reduce the burden related to CAD.

It is recommended that to be successful in reducing the mortality due to CAD in 21st century, as many high-income countries did during the last decade of 20th century, low and middle-income countries may need to develop new innovative population wide preventive strategies [66]. With the rapid advancement in tele-media access, new technologies provide the potential for more cost effective and efficiently delivered health care interventions [64] . One such promising technology is the mobile phone technology, referred as mHealth [65] which include text messaging, video messaging, video calling, and internet connectivity [66, 67].

Mobile phones support two-way synchronous conversation (voice calling) and durable textual communication (Short Message Service, SMS). Mobile phone text messaging has a great potential as a tool for improvement of preventative health care. It is easy to execute, low cost, and the service is available in all contemporary mobile phones. SMS widespread use, its ability to present succinct and instantaneous yet durable information makes text messaging suitable for a wide variety of health care management measures [66, 68]. Advantages of text messaging includes ready access of information when and wherever convenient to the patients [66] and the reliability of delivery (even if the phone is turned off when the message is delivered the patient will still receive it upon turning the phone on) [69]. Text messaging is particularly

suitable for behavioral interventions because it allows for in-the-moment, personally tailored health communication and reinforcement. Recent studies have found that periodic prompts, and reminders are effective methods to encourage and reinforce healthy behaviors [70-72]. Studies were conducted with the aims to manage depression as well as CAD risk factors behaviours using tele-based care management model [73, 74] incorporating Cognitive Behavior Therapy (CBT) counselling [73, 75]. The intervention comprises of telephonic session of CBT counselling, goal setting and motivational interviewing technique [73]. Study done in USA explored a mobile phone context aware system that can sense a person behavior and then provide a treatment platform that can positively reinforce adaptive behavior and provide support for changing those that contribute to depression [76]. The study was conducted on 8 participants and it showed promising results.

The number of mobile phone users in Pakistan reached 136.5 million mark at the end of March 2014, and this number continues to grow at a fast pace [77-79]. In 2011, the number of text messages exchanged in Pakistan jumped to 238 billion from 152 billion in 2010, illustrating the upwards trend in SMS usage [80]. Importantly, mobile phones also have huge penetration in rural areas of Pakistan. As a result, mHealth has the potential to deliver healthcare programs to the entire population of Pakistan.

Given the high prevalence of known major modifiable risk factors for CAD within the Pakistani population, there is an urgent need to develop sustainable interventions to help reduce these risk factors. It has been identified that there is a deficit in knowledge regarding CAD and its prevention in Pakistan, and in the context of the present health care system of Pakistan, with limited resources, competing priorities, and lack of will to fund preventive programs to reduce the burden of CAD it is now imperative to target preventive strategies that are affordable, feasible, and have the highest probabilities of success. The method of delivering health and lifestyle modification information on individual and community level should be affordable,

accessible, wide reaching and sustainable for a longer period which can improve health outcome. The effectiveness of utilizing SMS for psychological wellbeing program in combination of CAD modifiable risk factors management program is yet to be established. The outcome of such program could not only benefits psychological wellbeing to improve all aspects of health related quality of life (HRQOL), but also CAD risk factors. The intervention program could also show economic benefits over more traditional mode of delivery. We therefore undertook a novel approach to utilize a mHealth (mobile phone text message) program for patients who had sustained nonfatal cardiac events and also include their primary care givers in Pakistan. The inclusion of care-givers was mainly for two reasons, first, to observe the effectiveness of text message for prevention, second, to reinforce the health messages to their patients and vice versa, so it should be a bidirectional process of reinforcing the messages.

Objective

The aim of our clinical trial was to find out the effectiveness of text messages (SMS) as an intervention to promote positive lifestyle, targeted towards the known major risk factors attributed for the development of CAD, which could reduce the mortality rate in patients who suffered first ever CAD.

The Primary outcome measures mortality rate is defined as: mortality due to cardiac cause, composite cardiovascular mortality (stroke, myocardial infarction, or death from any cardiovascular cause) whichever occurs first. If the cause of death is unknown, that was recorded as ‘presumed cardiovascular death – cause unknown’, and readmission to a hospital due to CAD-related events.

Hypothesis:

Ha: mobile phone text messages promote healthy lifestyle among first ever patients of CAD and their primary care-givers, which will indirectly reduce the mortality rate among CAD patients.

Ha: mobile phone text messages can promote psychological wellbeing among first ever patients of CAD and their primary care-givers

CHAPTER 2:

Mobile phone-assisted lifestyle modifications for the prevention of coronary heart disease – randomized controlled single blinded clinical trial: protocol and descriptive analysis

CHAPTER 2: Mobile phone-assisted lifestyle modifications for the prevention of coronary heart disease – randomized controlled single blinded clinical trial: protocol and descriptive analysis

Title:

Mobile phone-assisted lifestyle modifications for the prevention of coronary heart disease – randomized controlled single blinded clinical trial: protocol and descriptive analysis

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Key Words:

Cardiovascular disease	(CVD)
Coronary Artery Disease	(CAD)
Diabetes Mellitus	(DM)
Disability-Adjusted Life-Years	(DALYs)
Electro Cardio-Gram	(ECG)
Generalized Anxiety Disorder	(GAD)
Hypertension	(HTN)
Karachi Institute of Heart Diseases	(KIHD)
Mobile Health	(mHealth)
Multimedia Message service	(MMS)
Myocardial Infarction	(MI)
National Institute of Cardiovascular Diseases	(NICVD)
Non Communicable Diseases	(NCD)
Patients Health Questionnaire	(PHQ)
Randomized Clinical Trial	(RCT)
Research Assistant	(RA)
Short Message Service	(SMS)
South Asian	(SA)
Tabba Heart Institute	(THI)
Usual care and Intervention group	(IG)
No-intervention group	(NIG)
World Health Organization	(WHO)

ABSTRACT:

Background:

Cardiovascular disease is the leading cause of deaths globally, especially in South Asian countries. Coronary Artery Disease (CAD) has a high prevalence in Pakistan and is a major cause of premature mortality in this country. Unhealthy diet, cigarette smoking, pollution, sedentary lifestyle, and psychological factors such as depression and anxiety are among the major modifiable risk factors. With the rapid advances and dissemination of mobile communication SMS messaging holds promise as an affordable, effective and far reaching means to effect behavioral changes in personalized health education, and health care management.

Objective:

This study aimed to explore the effectiveness of a mobile phone text messaging intervention program for improving major risk factors among CAD patients and their care-givers.

Methodology:

A prospective, randomized, controlled, single blinded clinical trial was conducted in 3 cardiac specific tertiary care hospitals in Karachi, Pakistan. Participants were patients who had their first cardiac events and their respective nominated care-givers. Patients and their care-givers were randomized into two groups, intervention (IG) or usual care group with no-intervention (NIG). For the participants in the IG daily health text messages were sent to their mobile phones, 5 days per week. Patients in both groups were followed up on an average of 3 to 6 monthly intervals for a total duration of 15 months.

Results:

A total of 2656 patients and 559 care-givers were recruited. Minimum follow-up was 180 days (range: 180 to 400 days). Mean age of patients was 52 years, of care-givers 39 years, 65% of patients and 36% of the care givers were male, 41% of patients and 70% of caregivers had formal education. Prevalence of smokers was 23% among patients and 9% among care givers, 33% of patients and 13% of care-givers had diabetes (DM), while 56% and 32%, respectively had hypertension (HTN). Physical activity levels were similar between patients and care givers. PHQ9 and GAD7 revealed that on average 28% of patients and 25% of care-givers were moderately to severe depressed, while 23% and 19%, respectively, suffered moderate to severe anxiety.

Conclusions:

We designed a prospective, randomized controlled, single blinded clinical trial in Pakistan to study the benefits of SMS targeting major modifiable risk factors associated with CAD. A novel approach was adopted to address the "Caregiver Strain" by recruiting caregivers as a parallel group along with their respective CAD patients. Results of the trial will assist in understanding the prognostic benefits of SMS among CAD patients and their care givers.

Key words: coronary artery diseases, caregivers, text messages, intervention, diet, physical activity, psychological stresses, clinical trial

TITLE:

Mobile phone-assisted lifestyle modifications for the prevention of coronary heart disease – randomized controlled single blinded clinical trial: protocol and descriptive analysis

SHORT TITLE: Mobile Phones for Preventing Heart Disease (MOPHD)

Or TEXT2PREVENT

INTRODUCTION:

Cardiovascular disease (CVD) including ischemic heart and cerebrovascular disease killed 17.5 million people globally in 2012[1, 2]. While CAD is the single largest cause of death in developed countries, it is also one of the leading causes of death in developing countries [1-3]. Three-quarters of global deaths due to CAD occurred in low and middle income countries, the majority of which were considered premature deaths (under the age of 70 years) [1-5]. The increasing trend of CAD in low and middle income countries (LMIC) is attributed to lifestyle and socio-economic changes, and increases in lifespan. Epidemiological studies in migrants of South Asian (SA) origin (i.e. from India, Pakistan and Bangladesh) living in the first world countries have consistently demonstrated disproportionately high incidences of CAD related mortality [7, 8, 11, 17, 26, 81-90]. In Pakistan CVD is a major public health problem [91-93], impacting on the nation's economy by disabling a significant proportion of the working age population.

The World Health Organization (WHO) identified four major preventable behavioral risk factors for CVD that are largely related to 21st century lifestyle: tobacco use, unhealthy diet, insufficient physical activity, and harmful use of alcohol[5]. These modifiable risk factors for CVD ultimately exert a heavy socioeconomic burden on all societies [5]. At least 80% of premature deaths from heart disease can be avoided by engaging in regular physical activity, avoiding tobacco use and second-hand tobacco smoke, choosing a diet rich in fruit and

vegetables, avoiding foods that are high in fat, sugar and salt, and maintaining a healthy body weight [30]. A recent study found that 4 out of 5 myocardial infarctions (MIs) in men could be prevented by following a healthy diet, being physical active (walking/bicycling ≥ 40 min/day and exercising ≥ 1 hr./week), moderate alcohol use (10 - 30 g/day), having no abdominal adiposity (waist circumference < 95 cm), and refraining from smoking[31]. In the last couple of decades, a sleuth of studies also identified depression, anxiety and other psychosocial factors including nonphysical stress as potent risk factors for CVD, associated with an increased risk of mortality [32-36].

If nothing is done to reduce the risk of chronic diseases in LMIC, an estimated US$84 billion of economic production between 2006 and 2015will be lost as a result of CVD and other morbidities caused by largely modifiable risk factors [94]. It is estimated that the cumulative losses due to non-communicable diseases (NCDs) under a "business as usual" scenario in LMIC would amount to US$ 7 trillion [2]. Whereas high-impact intervention to reduce the NCD burden would only cost around US$ 11.2 billion annually [2]. Many primary and secondary preventive strategies have failed to achieve desired goal [58, 59]. The WHO-PREMISE project showed that a significant number of patients fail to adopt healthy lifestyle habits after a major cardiovascular event, 12.5% of the studied patients continue to smoke, 38.4% do not comply with dietary advice, and 52.5% do not engage in regular physical activity [59]. The results of the WHO-PREMISE project underscore the need for novel strategies to improve compliance and persistence in risk factor modification measures.

Literature is replete with research outcomes on patient centered care, but little information is available on patients' informal care givers. Family care giving is defined as extensive care to the patients, without any financial benefits, by spouses, parents, and loved ones[51]. Caregivers are usually involved in direct assistances (e.g., helping in daily activities, medication, and lifestyle management), monitoring symptoms, maintaining physician

appointment and accompanying at physician clinic[51]. All these additional workloads put caregiver at "caregiver strain", which causes sleep disturbance, physical exhaustion, change in their personal plan, depression, anxiety, financial constraint, and poor self-rated health [52-55]. Family caregivers has an important role and it has been recognized, but high physical, and psychosocial demand expose them at greater risk of ill health, even mortality due to CVD [54, 56]. Intervention has been recommended for the wellbeing of the caregiver [57], but, to our knowledge, none has been developed and implemented.

With the rapid advancement in tele-media access, new technologies have been tried to more cost effective and efficiently deliver health care measures [64]. One of which is the mobile phone technology, referred as mHealth [65] which include text messaging, video messaging, video calling, and internet connectivity [66, 67].

Mobile phones support two-way synchronous conversation (voice calling) and durable textual communication (Short Message Service, SMS). Mobile phone text messaging in particular has a great potential as a tool for improvement of preventative health care. It is easy to execute, low cost, and the service is available in all contemporary mobile phones. SMS widespread use, its ability to present succinct and instantaneous yet durable information makes text messaging suitable for a wide variety of health care management measures [66, 68]. Emphasis of test messaging advantages include ready access of information when and where ever convenient to the patients [66], reliability of delivery (even if the phone is turned off when the message is delivered the patient will still receive it upon turning the phone on) [69]. Text messaging is particularly suitable for behavioral interventions because it allows for in-the-moment, personally tailored health communication and reinforcement. Recent studies have found that periodic prompts and reminders are effective methods to encourage and reinforce healthy behaviors [70, 71].

The number of mobile phone users in Pakistan reached 136.5 million mark at the end of March 2014, and this number continues to grow at a fast pace [77-79]. In 2011, the number of text messages exchanged in Pakistan jumped to 238 billion from 152 billion in 2010, illustrating the upwards trend in SMS usage [80]. Importantly, mobile phones also have huge penetration in rural areas of Pakistan. As a result, mHealth has the potential to deliver healthcare programs to the entire population of Pakistan.

In Pakistan, where there is a high and increasing prevalence of CVD, and the majority of the population lacks substantive knowledge on risk reduction related life style modification measures [62, 63], effective low cost educational strategies are greatly in need. We have therefore undertaken to design a mHealth program for patients who had sustained nonfatal cardiac events and also include their primary care givers in the study.

METHODOLOGY:

Trial Design

The study was designed as a randomized, controlled, single blinded clinical trial

Participants

The first group of subjects comprised cardiac patients who had suffered their first *non-fatal* cardiac event related to CAD, and admitted in one of our participatory study hospital. The second group of study subjects consisted of primary care-givers to the cardiac patients. Primary care giver is defined as a spouse, adult child or parents of the patient, designated by the patient[51]. Care-givers provide a wide range of unpaid care and assistance, such as, bathing, dressing, feeding, toileting, helping with incontinence, assisting with mobility, cooking, house cleaning, handling finance, transport to health professional appointments and overseeing or assisting with medication [95].

Eligibility criteria for participants

Subjects were recruited if they were in a sound state of mind, i.e. no self-reported symptoms of psychosis, delirium, and dementia, and were able to communicate in a coherent way, willing to participate in the study, had stable cardiac status at discharge, owned a personal mobile phone with a personal SIM, were willing to retain the same SIM during the study period (or were willing to inform the investigators if their phone number changed), understood the basic operations of a mobile phone, were able to read text messages, and did not have any significant life-threatening co-morbidities (such as terminal cancer or end stage renal disease). Subjects were excluded if they did not own a mobile phone and were unwilling to acquire one, were pregnant females, or were below the age of 18 years old.

Study Sites

The study was conducted at the three tertiary care cardiac specific hospitals with basic and advanced facilities for cardiac care in Karachi: National Institute of Cardiovascular Diseases (NICVD), Karachi Institute of Heart Diseases (KIHD), and Tabba Heart Institute

(THI). The majority population of Karachi falls into the catchment of these three cardiac hospital.

Intervention

Mobile phones were used to deliver positive behavioral change/lifestyle modification health messages to the intervention group (IG) by SMS. The primary and secondary prevention programs for CAD were based on guidelines developed by WHO and the National Heart Foundation of Australia [32, 33, 96]. The pool of health messages was developed by the study investigators. The messages were pilot tested in 300 subjects and assessed for their level of comprehensibility and comfort. Messages that were not easily understood were re-worded to eliminate ambiguity.

Some of the messages sent to the IG in lay language are as follows;

- Quit tobacco use, reduce the amount smoked, or do not start the habit;
- Smoking tobacco is injurious to your health, especially for heart.
- Be physically active (at least 30 minutes on most week days);
- If you are fit, climb the stairs instead of taking the escalator or elevator, get off the bus, a stop earlier and walk,
- Park the car further away from your destination, walk to the corner store, bank and post office, stand while talking on the mobile phone
- Make healthy food choices;
- Increase vegetable intake; they are a healthy source of vitamins, minerals & fiber.
- Reduce your total intake of fats, use sugars and sweets sparingly
- Four golden rules to help avoid high blood pressure – weight control, positive lifestyle, healthy diet, medical check up
- Being depressed, anxious, helpless and negative thoughts will make you weak, and away from a healthy life.

Messages were also sent to subjects in the IG to remind them of their appointment schedule and to adhere to their prescribed medications. Messages were limited to 160 characters and were phrased in layman terminology. During the initial 6 months following enrollment, one message was delivered every weekday, targeting one risk factor per day in a cyclical fashion. After 6 months, the frequency was increased to 2 or 3 messages per day, 5 days per week, each targeting a different risk factor. In contrast, the NIG received general greeting messages, including thanking them for being in the study, and reminders about their follow-up appointments. These messages were sent out fortnightly.

The communication was of a two-way nature. Participants were encouraged to send general enquiries about major risk factors by SMS. Javed Ismail (JI) responded to their queries within 48 hours. Voice calls were also responded to where possible. Via SMS queries from the IG were replied in detail, whereas lifestyle modifications related queries from the NIG were not answered specifically. Instead, they were advised to consult their treating physician. Members from either group with queries relating to specific health conditions including medications and symptoms were directed to their treating physicians. The study was not designed to evaluate the pharmacologic therapies administered to the patients by their treating physicians and did not interfere with their routine medical care. Information derived from this study was not made available to the treating health care professionals of the participants.

Primary Outcomes

The Primary outcome measure was mortality due to cardiac cause, composite cardiovascular mortality ('stroke, myocardial infarction, or death from any cardiovascular cause', whichever occurs first. If the cause of death is unknown, that was recorded as 'presumed cardiovascular death – cause unknown'), and readmission to hospital due to CAD related events.

Secondary Outcomes

The Secondary outcomes were measured differences in the quantitated values of the selected risk factors, such as, blood pressure, quit smoking, chest pain, physical activity, dietary habits, depression and anxiety, and selected biomarkers, such as, lipid profile, and HbA1c, from baseline at every subsequent follow up, between the group and within the group.

Sample Size

The sample size was calculated on the basis of the dichotomous primary outcome variables (mortality and readmission). Previous studies have shown that mortality due to cardiovascular diseases in Pakistan was 12% to 29% [97, 98]. To capture the least prevailing associated risk factor, the sample size was calculated based on a mortality of 15% due to CVD. With 80% power, 5% significance level, and 10% difference (from 15% to 5%) in the mortality rate between groups, the calculated sample size was 700 patients in each group. After assuming a 10% attrition rate, the final sample size was determined as 770 patients in each group (1540 total). Because there was one primary caregiver for every patient, the same sample size was assumed for caregivers. As a result, the total sample size deemed appropriate was 3080 with 1540 subjects each for patients and caregivers.

Randomization

Patients were randomly assigned to the *intervention group* (IG) or the *no-intervention group* (NIG). The IG (patients and their respective care-givers) received lifestyle modification education via text messages. The NIG (patients and their respective care-givers) received "neutral messages" consisting of greeting/salutation, and reminder of follow-up dates and time, once per week.

Sequence generation and allocation concealment mechanism

A randomization list of 100 subjects for each site was generated in STATA software, with equal numbers of participants in the IG and NIG. The subjects were randomized by their study registration number. The list was kept with one of the study investigators Javed Ismail (JI) who supervised the data collection but did not have direct personal contact with the subjects at the time of baseline recruitment. RAs gave subjects a consecutive study registration number, and sent their questionnaire with the allotted study registration number to the study office. Here, JI assigned to each patient a group (IG or NIG) as per the randomization list. The delivery of behavioral change SMS text messages, and replies to the queries of the study subjects were done by JI.

Blinding

RAs were blinded from participant's assigned group till close of the trial. Whereas, JI was blinded to the baseline health status of the subjects. At follow-ups RAs were instructed not to inquire about health messages type and frequencies from participants

Study Variables

Where possible, data were collected as continuous variables. Continuous variables were converted to categorical variables during the analysis phase where necessary. Information was collected relating to socio-demographics, cigarette smoking, use of smokeless tobacco, physical activity, leisure time physical activity, dietary habits (especially consumption of dietary fat), anthropometric measurements, co-morbidities (including HTN, DM, angina pectoris), family history of CAD, body mass index (BMI), anxiety, depression and general health, using a tailored questionnaire designed specifically for the purpose of the study (food frequency questionnaire), and international validated questionnaire (International Physical Activity Questionnaire [IPAQ] short version, Patients Health Questionnaire [PHQ9] for

depression, and Generalized Anxiety Disorder [GAD7]. The questionnaires are available in supplementary section online.

Baseline Data Collection

Patients were approached by research assistants (RAs) during their inpatient stay for enrolment into the study. Data derived from and collected for this study were not made available to the patients' physicians. The study data were collected from June 2012 to December 2013. A detailed questionnaire was developed in English, translated into Urdu by a certified translator, then back into English to ensure accuracy and to maintain the essence of the questions. A trained RA administered a structured questionnaire to each participant at baseline. The questionnaire was designed to collect information relating to socio-demographics, health status, family history and CAD risk profile. Dietary patterns were assessed on a food frequency format that was developed by JI relevant to the local diet, and implement by him in one of his previous study [99]. Physical activity levels were assessed using a short version of the IPAQ and household activity portion of leisure time physical activities (LTPA) questionnaire of Minnesota heart health program [100, 101]. As defined in IPAQ, three levels of physical activities were assessed. *(Daily) walk* is defined as walking at work and at home, walking to and travel from place to place, and any other walking that individual might do solely for recreation, sport, exercise or leisure; *moderate physical activities* were activities that take moderate physical effort and make individual breathe somewhat harder than normal, like, carrying light weight; *vigorous physical activities* were activities that take hard physical effort and make individual breathe much harder than normal, like, heavy lifting. Depression and Anxiety were evaluated by PHQ 9 (Urdu version) and GAD 7 (Urdu version) questionnaires [102].

RAs were provided with extensive training by the principal investigator (JI) on how to frame each question and measure height, weight, heart rate, and blood pressure. An experienced

laboratory technician drew venous blood samples from subjects following a 12-hour overnight fast. The blood samples were sent to the laboratory (Dr. Essa's Laboratory and diagnostic center, Karachi, Pakistan) for lipid profile and HbA1c.

Follow-Up Data Collection

The first follow-up was made at six months (range: 180 days – 400 days) following enrolment. Subsequent follow-ups occurred at 90 days' intervals. Questionnaire was administered at follow-up and blood tests for laboratory investigations were performed until funds were available to offer free investigations.

Ethical Considerations

Ethics approval for the study was granted by the Human Ethics Review Board of Macquarie University. Approvals were also obtained from the institutional review boards of each participating hospital. A detailed consent form was developed for the patients explaining the objectives of the study and their rights. The informed consent form was drafted in English, translated into Urdu by certified translators, then back into English to ensure accuracy. At enrollment, participants were asked to read the informed consent form or it was read to them if they had difficulty in reading. Participants were encouraged to ask questions for clarification and were told that their participation was voluntary and that they could withdraw at any time during the course of the study.

Statistical methods

Intention to treat was the primary approach for the analysis. Allowances were made for attrition in the sample size estimation but analyses were performed on the data with and without missing values.

A descriptive analysis was performed to examine the socio-demographic characteristics of the study population. Student's t test, Chi square and Fisher's exact tests were conducted to determine the homogeneity of demographic and clinical characteristics of the IG and NIG.

t-test was carried out to determine within- and between-group differences in measured modifiable risk factors for CAD.

The data was entered using IBM SPSS Data Collection software and analyzed through SPSS statistical analysis software (IBM® SPSS® statistics, version 21, IBM Corporation, USA)

RESULT:

Between June 2012 to December 2013, total of 2656 patients and 559 caregivers were enrolled. Mean follow-up period was 180 days (range, 180 days to 400 days). Patients and care-givers participation and their breakdown is illustrated in figure 1.

Baseline Socio-demographic characteristics (Table 1)

Demographic and baseline characteristics were similar between groups. The majority of patients (65%) from all participating sites were male, while female represented the larger proportion among caregivers (approximately 65%). The majority of patients and caregivers (97 % and 82%, respectively) were married, and more care givers had formal education (see table 1).

Baseline prevalence of major cardiovascular risk factors (Table 2)

Between group (IG and NIG) there were no difference in the prevalence of risk factors among patient and care-givers. As a whole (IG and NIG) the patients have a higher prevalence of smokers than care-givers (23% vs 09%, p = .35). Similar trend exists for the prevalence of DM and HTN between patients and care-givers, 33% vs 13%, (p = .86) and 56% vs 32% (p = .98), respectively.

Baseline laboratory investigations (Table 3a and 3b)

Laboratory investigations were obtained from 273 patients in IG and 282 patients in NIG, and from 128 caregivers in IG as well as 131 caregivers in NIG. The laboratory parameters were similar between IG and NIG, for patients and care-givers. The baseline lipids

and glycemic profiles are shown in table 3a. Medication prescribed to patients are shown in table 3b.

Baseline physical activities (Table 4)

The baseline physical activity levels were assessed by using IPAQ and WHO household activity of 17 activity parameters [100]. Participation in vigorous physical activities were reported by 19% of patients and 15% of caregivers, whereas moderate physical activities by 56% and 41% of patients and caregivers, respectively. Thirty-seven percent of patients and 34% of caregivers also engaged in daily walk. Details of intensity and duration of physical activities, and sedentary time were presented in table 4.

Table 1: Baseline comparison of Socio-Demographic characteristics of intervention and non-intervention groups of patients and care givers

Variables	PATIENTS (2656)		p	CAREGIVER (559)		p
	IG* (1352) n (%)	NIG$^{\beta}$ (1304) n (%)		IG* (279) n (%)	NIG$^{\beta}$ (280) n (%)	
Study Sites			.95			.49
National Inst. C.V.D	814 (60.2)	792 (60.7)		113 (40.5)	114 (40.7)	
(NICVD)	489 (36.2)	464 (35.6)		143 (51.3)	150 (53.6)	
Kar. Inst. Heart Dis. (KIHD)	049 (03.6)	048 (03.7)		023 (08.2)	016 (05.7)	
Tabba Heart Dis. (THI)						
Gender			.35			.10
Male	892 (66.0)	838 (64.3)		95 (34.1)	114 (40.7)	
Female	460 (34.0)	466 (35.7)		184 (65.9)	166 (59.3)	
Age (Yrs.)						
Mean (± SD)	52.3 (10.3)	52.2 (10.3)	.73	39 (11)	39.2 (11.3)	.83
Ethnicity			.19			.40
Mohajir	837 (61.9)	770 (59)		198 (71)	207 (73.9)	
Punjabi	149 (11)	175 (13.4)		25 (09)	21 (07.5)	
Sindhi	057 (04.2)	060 (04.6)		05 (01.8)	05 (01.8)	
Balochi	024 (01.8)	013 (01)		04 (01.4)	00 (0)	
Pushto	113 (08.4)	116 (08.9)		15 (05.4)	18 (06.4)	
Marital Status			.54			.48
Married	1315 (97.3)	1272 (97.5)		236 (84.60)	225 (80.40)	
Unmarried	13 (01.0)	15 (01.20)		037 (13.30)	045 (16.10)	
Divorced/widowed/separated	09 (0.70)	09 (0.70)		002 (0.70)	005 (1.80)	
Formal Education	558 (43.50)	532 (40.80)	.35	199 (71.30)	188 (67.10)	.49
Level of Education			.88			.09
Primary	132 (09.80)	125 (09.60)		19 (06.80)	19 (06.80)	
Secondary	230 (17)	216 (16.60)		63 (22.60)	65 (23.20)	
Higher Secondary	068 (05)	056 (04.30)		22 (07.90)	33 (11.80)	
Bachelors	093 (06.90)	081 (06.20)		72 (25.80)	46 (16.40)	
Master	022 (01.60)	022 (01.70)		14 (05)	19 (06.80)	
Doctor	003 (0.20)	002 (0.20)		02 (0.70)	00 (0)	
Employment	620 (45.90)	589 (45.20)	.30	117 (41.90)	119 (42.50)	.19
Occupation			.95			.30
Private Job	435 (32.20)	422 (32.40)		66 (23.70)	79 (28.20)	
Government Job	072 (05.30)	068 (05.20)		21 (07.50)	23 (08.20)	
Own Business	075 (05.50)	066 (05.10)		18 (06.50)	10 (03.60)	
Nature of Job			.23			.77
Desk Job	228 (16.90)	235 (18)		39 (14)	45 (16.10)	
Physical	281 (20.80)	282 (21.60)		43 (15.40)	43 (15.40)	
Mix of Desk and Physical	079 (05.80)	055 (04.20)		29 (10.40)	23 (08.20)	

* Intervention Group - $^{\beta}$ Non-Intervention Group - (P value significance level at 0.05)

Table 2: Baseline comparison of prevalence of major CAD Risk factors of intervention and non-intervention groups' patients and caregivers

Variables	PATIENTS (2656)		p	CAREGIVER (559)		p
	IG* n (1352) (%)	NIG$^{\beta}$ n (1304) (%)		IG* n (279) (%)	NIG$^{\beta}$ n (280) (%)	
Family History of CAD	463 (35.10)	418 (32.80)	.22	146 (52.90)	132 (48.40)	.28
Father	222 (40)	211 (42.40)	.43	082 (51)	064 (45.40)	.31
Mother	178 (32.10)	155 (31.10)	.74	075 (46.90)	060 (42.60)	.45
Brother	138 (24.90)	134 (26.90)	.45	026 (16.30)	026 (18.40)	.61
Sister	056 (10.10)	047 (9.40)	.72	009 (05.60)	008 (05.70)	.98
Consanguineous Marriage (Parents	357 (30)	346 (29.4)	.75	70 (26.7)	71 (27.7)	.79
Dyslipidemia	136 (10.2)	130 (10.10)	.94	34 (12.30)	32 (11.70)	.83
Diabetes Mellitus	450 (33.40)	429 (33.10)	.86	38 (13.70)	35 (12.60)	.70
Duration of DM mean, (± SD)	8.21 (±6.70)	8.40(±6.54)	.69	7.61 (±5.60)	6.28 (±5.19)	.29
Hypertension	764 (56.5)	741 (56.80)	.98	89 (32)	89 (31.80)	.13
Duration of Hypertension Mean – (± SD)	6.32 (±6.41)	6.29 (±5.93)	.92	6.73 (±5.28)	5.33 (±4.43)	.06
Smoking tobacco (cig.)	307 (22.70)	305 (23.40)	.25	26 (09.30)	24 (08.60)	.35
Duration of Smoking (yrs.) Mean - (± SD)	23.6 (±12.7)	22.8(±13.2)	.81	12.6 (±11.1)	15.3 (±11.3)	.39
Quantity of Cigarette/day Mean - (±SD)	16.8 (±12.5)	15.6 (±10.9)	.19	10.8 (±6.1)	12.5 (±6.8)	.35
Ex-Smoker	71 (05.40)	65 (05.10)	.70	03 (01.10)	04 (01.40)	.34
Smokeless Tobacco	297 (22)	289 (22.21)	.76	23 (08.20)	37 (13.30)	.06
Paan	187 (50)	176 (51.60)	.66	18 (43)	24 (53.30)	
Naswar	067 (17.90)	074 (21.80)	.19	02 (04.80)	04 (09)	
Systolic Blood Pressure Mean - (± SD)	128 (±23.38)	128 (±24.02)	.88	138 (±27)	130 (±31.7)	
Diastolic Blood Pressure Mean - (± SD)	77.8 (±13.4)	78.5 (±13.9)	.21	76.6 (±10.5)	76.6 (±10.5)	.58
Pulse /min. Mean - (±SD)	78.9 (±11.8)	79.4 (±12.5)	.37	81.5 (±10.9)	80.4 (±10.0)	.52
Alcohol	13 (1.0)	09 (0.70)	.50	01 (0.40)	02 (0.70)	.84
Major Symptoms						
Dizziness	570 (43.30)	530 (42)	.49			
Sweating	944 (71.70)	905 (71.70)	.99			
Shortness of Breath	818 (62.20)	766 (60.70)	.46			
Nausea/Vomiting	557 (42.30)	537 (42.60)	.89			
Anxiety/Discomfort	1012 (76.90)	947 (75.10)	.28			

* Intervention Group - $^{\beta}$ Non-Intervention Group - (Chi Sq. to compare proportion: t-test to compare mean: P value significance level at 0.05)

Table 3a: Baseline comparison of Laboratory Investigations of intervention and non-intervention groups of patients and caregivers

Variables	PATIENTS (2656)		p	CAREGIVER (559)		p
	IG n = 273 Mean (±SD)	NIG n = 282 Mean (±SD)		IG n = 128 Mean (±SD)	NIG n = 131 Mean (±SD)	
Serum Cholesterol (mg/dl)	174.7 (±33.9)	172 (±35.7)	.45	184 (±32.6)	190 (±33.8)	.15
HDL (mg/dl)	42.4 (±04.3)	42.3 (±04.7)	.70	42.4 (±04.2)	42 (±04.4)	.53
LDL (mg/dl)	100.8 (±31.4)	98.8 (±35.2)	.50	115 (±32.3)	119 (±33.3)	.33
VLDL (mg/dl)	31.50 (±17.8)	31.2 (±17.6)	.93	26.6 (±11.1)	28.9 (±16.6)	.18
Triglycerides (mg/dl)	158.9 (±90.7)	155.3 (±88)	.72	133 (±55.5)	144.8(±83.2)	.17
Total Lipids (mg/dl)	823.5 (±120)	815.8 (±117)	.51	822 (±92.2)	838 (±109.4)	.19
Cholesterol: HDL Ratio (mg/dl)	04.2 (±18)	04.2 (±01.5)	.81	4.5 (±01.4)	04.7 (±01.4)	.30
HbA1c (mg/dl)	06.7 (±01.9)	06.7 (±01.8)	.87	5.9 (±01.3)	05.8 (±01.1)	.89

* Intervention Group - β Non-Intervention Group - (t-test to compare mean: P value significance level at 0.05)

Table 3b: Baseline comparison of Medication of intervention and non-intervention groups of patients

Variables	PATIENTS (2656)		p
	IG* n = 1258 (%)	NIGβ n = 1232 (%)	
Aspirin	1204 (96)	1174 (95.3)	.62
Antiplatelet	1076 (85.5)	1052 (85.5)	.96
Antithrombotic	63 (05)	0057 (04.6)	.66
Lipid Lowering	890 (70.7)	0878 (71.4)	.67
Beta Blocker	886 (70.5)	0854 (69.5)	.60
ACE Inhibitor	450 (35.5)	0411 (33.1)	.24
Ca Channel Antagonist	562 (44.4)	0558 (44.9)	.76
Diuretics	126 (10)	0156 (12.6)	.91
Nitrates	506 (40)	0508 (41)	.59
Insulin	50 (04)	0062 (05)	.15
Oral antidiabetics	159 (12.5)	0163 (13.1)	.31

* Intervention Group - β Non-Intervention Group - (t-test to compare mean: P value significance level at 0.05)

Tab 4: comparison of Baseline Physical activities of intervention and non-intervention groups of patients and caregivers

Variables	PATIENTS (2656)				p	CAREGIVER (559)				p
	IG* (1352)		NIG$^{\beta}$ (1304)			IG* (279)		NIG$^{\beta}$ (280)		
	n	/mean (±SD)	n	/mean (±SD)		n	/mean (±SD)	n	/mean (±SD)	
Vigorous Physical Activity*										
Days/wk. –	198	3.72 (2.3)	198	3.83 (2.5)	.60	49	4.76 (2.40)	58	4.76 (2.32)	.99
Duration/day (minutes)	198	161.9 (153)	198	177.7 (167)	.31	49	205 (136)	58	189 (143)	.52
Duration/Wk. (minutes)	197	861 (1242)	196	1117 (1954)	.12	48	989 (913)	58	1368 (1852)	.20
Moderate Physical Activity$^{\beta}$										
No. Days/wk.	555	5.60 (01.6)	535	5.43 (1.7)	.12	160	6.24 (1.2)	154	06.2 (1.2)	.87
Duration/day	555	225 (196)	535	213 (194)	.29	160	269 (184)	153	249 (170)	.30
Duration/Wk.	551	1209 (1263)	531	1207 (1264)	.98	157	1643 (1417)	153	1474 (1205)	.26
Walk days/wk.										
No. Days/wk. mean (± SD)	527	5.96 (1.45)	457	5.74 (1.70)	.30	98	5.81 (1.78)	93	5.57 (2.0)	.39
Duration/day (minutes)	527	38.62 (47)	457	38.11 (49)	.16	98	46.7 (58.2)	93	38.3 (42.2)	.25
Duration/Wk. (minutes)	523	278 (600)	449	265 (478)	.36	98	278 (396)	93	218 (280)	.26
Sitting time/wk. (minutes)	1349	404.8 (183)	1305	405.4 (187)	.97	279	403.2 (196)	280	385 (193)	.26
Climb floor/day (average 15 stairs)	1043	1.81 (0.91)	987	1.76 (0.83)	.91	231	1.77 (1.09)	226	1.79 (0.84)	.85
Grocery shopping/month	671	7.34 (4.70)	657	7.38 (2.70)	.86	174	8.16 (3.12)	145	9.38 (1.33)	.16
Make Bed/month	030	8.60 (4.90)	027	9.11 (5.1)	.70	12	10 (4.67)	15	6.40 (5.30)	.07
Laundry/month	159	7.84 (5.82)	162	7.68 (3.44)	.76	115	9.30 (3.21)	95	8.59 (3.35)	.12
Prepare Meal/month	239	11.57 (13.4)	228	10.70 (7.20)	.38	149	11.6 (8.20)	121	10.90 (2.90)	.33
Wash Dishes/month	199	10.60 (2.98)	182	10.62 (2.92)	.94	142	11.23 (2.34)	107	11.24 (2.26)	.95

* Intervention Group - $^{\beta}$ Non-Intervention Group **- (t-test was conducted and P value significance level at 0.05)**

Baseline dietary consumption (Table 5a and 5b)

Dietary preferences of the study subjects were measured by a food frequency questionnaire, which has been designed by including major local food categories consumed by the targeted population. In our food frequency questionnaire, healthy food items (fruits, vegetables, white meat etc.) were randomly placed with unhealthy food items (food items containing high saturated fat contents), to capture the true responses of the participants without leading them any idea for healthy and unhealthy dietary pattern. Food preferences among patients and care givers were similar. Patients and care-givers (IG and NIG) uniformly favor a diet of rice, beans/lentils, cooked vegetables, chicken, biryani (rice with meat and spices cooked in oil/saturated fat), potatoes, plain yogurt, eggs, fish, beef, bakery products, milk dessert and soft drinks (see table 5a and 5b.)

Baseline prevalence of depression and anxiety (Table 6)

Patients and caregivers (in both IG and NIG) showed similar findings for depression and anxiety on baseline assessment. PHQ 9 showed that 71.5% of patients (IG + NIG) and 75% of care-givers (IG + NIG) were mildly depressed while 28% vs 25%, respectively, reported moderate to severe depression. Similar trends were observed for anxiety (see table 6).

Table 5a: Food preferences of intervention and non-intervention groups of patients

Table : Food preferences of the study subjects

	Intervention (Pts. n=1352)			Non-Intervention (Pts. n=1304)		
Food Items	Percent use n (%)	1-2 s/mnths n (%)	1-2 s/wk n (%)	Percent use n (%)	1-2 s/mnths n (%)	1-2 s/wk n (%)
Eggs (whole)	872 (64.50)	236 (17.45)	546 (40.38)	860 (65.95)	228 (17.48)	568 (43.55)
Eggs (White)	186 (13.76)	53 (3.92)	106 (7.84)	192 (14.72)	54 (4.14)	113 (8.66)
Paratha	809 (59.84)	158 (11.68)	341 (25.22)	512 (39.26)	174 (13.34)	314 (24.07)
Naan	693 (51.26)	459 (33.94)	186 (13.75)	688 (52.76)	454 (34.81)	182 (13.95)
Halwa Puri	556 (41.12)	439 (32.47)	111 (8.21)	536 (41.10)	428 (32.82)	96 (7.36)
Milk(whole)	221 (16.35)	48 (3.55)	96 (7.10)	233 (17.87)	55 (4.21)	93 (7.13)
Milk(Skim)	569 (42.09)	59 (4.36)	300 (22.18)	456 (34.97)	74 (5.67)	278 (21.31)
Cream	135 (18.25)	69 (5.10)	50 (3.69)	147 (11.28)	74 (9.64)	55 (4.21)
Milk Dessert	1018 (75.30)	782 (57.84)	218 (16.12)	971 (74.47)	753 (57.74)	205 (15.72)
Ice Cream	632 (46.75)	534 (39.49)	92 (6.80)	616 (47.24)	517 (39.64)	98 (7.51)
Yogurt(Plain)	1031 (76.26)	177 (13.09)	796 (58.87)	998 (76.54)	183 (14.03)	770 (59.04)
Yogurt (Sweet)	640 (47.34)	490 (36.24)	133 (9.83)	649 (49.74)	487 (37.34)	142 (10.88)
Kata Kat	880 (65.09)	718 (53.10)	147 (10.87)	843 (64.65)	688 (52.76)	143 (10.96)
Margarine	424 (31.37)	119 (8.80)	264 (19.52)	401 (30.76)	109 (8.35)	258 (19.78)
Goat Meat	336 (24.86)	133 (9.83)	194 (14.34)	326 (25)	148 (11.34)	172 (13.19)
Beef	885 (65.46)	141 (10.42)	730 (53.99)	892 (68.41)	133 (10.19)	748 (57.36)
Chicken	1232 (91.13)	193 (14.2)	1004 (74.26)	1196 (91.72)	193 (14.80)	981 (75.23)
Fish	921 (68.13)	761 (56.28)	151 (11.16)	900 (69.02)	742 (56.90)	151 (11.57)
Prawn	47 (3.48)	40 (2.95)	07 (.52)	82 (6.29)	69 (5.29)	13 (0.99)
Organ Meat	629 (46.53)	582 (43.04)	47 (3.47)	628 (48.16)	588 (45.09)	39 (2.99)
Burgers	404 (29.89)	351 (25.96)	45 (3.32)	420 (32.21)	347 (26.61)	61 (4.67)
Vegetables Cooked	1303 (96.38)	29 (2.14)	1146 (84.76)	1260 (96.63)	37 (2.83)	1109 (85.04)
Potatoes	1196 (88.47)	108 (7.99)	993 (73.44)	1149 (88.11)	101 (7.74)	967 (74.15)
Vegetable Uncooked	1083 (80.10)	129 (9.54)	852 (63.0)	1045 (80.14)	158 (12.11)	810 (62.11)
Biryani/Palao	1212 (89.65)	942 (69.67)	259 (19.15)	1178 (90.34)	885 (67.87)	280 (21.47)
Beans/Lentils	1327 (98.15)	33 (2.44)	1210 (89.49)	1258 (96.48)	24 (1.84)	1166 (89.41)
Fruits	1203 (88.98)	194 (14.34)	887 (65.60)	1128 (86.51)	192 (14.72)	819 (62.80)
Fresh Fruit Juice	733 (54.22)	546 (40.38)	158 (11.68)	721 (55.30)	555 (42.56)	147 (11.27)
Soft Drinks	914 (67.60)	720 (53.25)	172 (12.72)	910 (69.79)	702 (53.83)	189 (14.49)
Bakery Products	926 (68.50)	609 (45.04)	261 (19.30)	838 (64.27)	563 (43.17)	213 (16.33)
Sweets (Mithai)	742 (54.88)	679 (50.22)	58 (4.28)	654 (50.16)	639 (49)	68 (5.21)
Fried Snacks	772 (57.10)	618 (45.71)	145 (10.72)	767 (58.28)	616 (47.23)	147 (11.27)
Dried Fruits (Nuts)	79 (5.85)	59 (4.36)	19 (1.40)	60 (4.61)	45 (3.45)	14 (1.07)
Chocolates	92 (6.80)	53 (3.92)	35 (2.58)	70 (5.37)	39 (2.99)	26 (1.99)
Rice (plain)	1164 (86.09)	149 (11.02)	788 (58.28)	958 (73.47)	149 (11.42)	789 (60.50)
Salad	497 (36.77)	58 (4.28)	420 (31.06)	505 (38.73)	68 (5.21)	418 (32.05)

Table 5b: Food preferences of intervention and non-intervention groups of care-givers

Table : Food preferences of the study subjects

Food Items	Intervention (Caregivers) (n=279)			Non-Intervention(Caregivers) (n=280)		
	Percent use n (%)	1-2 s/mnths n (%)	1-2 s/wk n (%)	Percent use n (%)	1-2 s/mnths n (%)	1-2 s/wk n (%)
Eggs (whole)	229 (82.03)	56 (20.07)	145 (51.97)	233 (83.21)	57 (20.35)	152 (54.28)
Eggs (White)	38 (13.62)	14 (5.01)	19 (6.81)	44 (15.71)	15 (5.35)	19 (6.78)
Paratha	223 (79.93)	54 (19.3)	95 (34.05)	208 (74.28)	52 (18.57)	95 (33.92)
Naan	180 (64.52)	123 (44.08)	49 (17.56)	195 (69.64)	119 (42.50)	65 (23.21)
Halwa Puri	133 (47.67)	105 (37.63)	27 (9.67)	155 (55.35)	125 (44.64)	28 (10)
Milk(whole)	74 (26.52)	25 (8.96)	27 (9.67)	69 (24.64)	22 (7.85)	29 (10.35)
Milk(Skim)	91 (32.62)	17 (6.09)	41 (14.69)	115 (41.07)	27 (9.64)	60 (21.42)
Cream	34 (12.19)	16 (5.73)	8 (2.86)	54 (19.28)	31 (11.07)	19 (6.78)
Milk Dessert	232 (83.15)	177 (63.44)	46 (16.48)	235 (83.92)	176 (62.85)	53 (18.92)
Ice Cream	174 (62.37)	136 (48.74)	37 (13.26)	186 (66.42)	136 (48.57)	49 (17.5)
Yogurt(Plain)	224 (80.28)	45 (16.12)	153 (54.83)	231 (82.5)	60 (21.42)	161 (57.5)
Yogurt (Sweet)	140 (50.18)	108 (38.70)	27 (9.67)	151 (53.92)	120 (42.85)	27 (9.64)
Kata Kat	210 (75.27)	160 (57.34)	49 (17.56)	206 (73.57)	152 (54.28)	52 (18.57)
Margarine	134 (48.03)	37 (13.26)	73 (26.16)	142 (50.71)	40 (14.28)	78 (27.85)
Goat Meat	76 (27.24)	33 (11.82)	40 (14.33)	79 (28.21)	32 (11.42)	44 (15.71)
Beef	190 (68.10)	43 (15.41)	142 (50.89)	214 (76.42)	39 (13.93)	172 (61.43)
Chicken	266 (95.34)	52 (18.63)	199 (71.32)	267 (95.35)	49 (17.5)	209 (74.64)
Fish	199 (71.32)	160 (57.34)	38 (13.62)	216 (77.14)	170 (60.71)	45 (16.07)
Prawn	22 (7.89)	19 (6.81)	1 (0.35)	28 (10)	26 (9.28)	2 (0.71)
Organ Meat	151 (54.12)	141 (50.53)	08 (2.86)	157 (56.07)	150 (53.57)	6 (2.14)
Burgers	172 (61.64)	131 (46.96)	37 (13.26)	163 (58.21)	126 (45)	33 (11.78)
Vegetables Cooked	267 (95.70)	06 (2.15)	200 (71.68)	267 (95.35)	08 (2.85)	216 (77.14)
Potatoes	264 (94.63)	17 (6.09)	192 (68.81)	261 (93.21)	10 (3.57)	209 (74.64)
Vegetable Uncooked	253 (90.68)	28 (8.60)	164 (58.78)	252 (90)	30 (10.71)	171 (61.07)
Biryani/Palao	269 (96.42)	172 (61.64)	89 (31.89)	270 (96.42)	172 (61.42)	92 (32.85)
Beans/Lentils	277 (99.28)	15 (5.37)	227 (81.36)	273 (97.5)	12 (4.28)	230 (82.14)
Fruits	257 (92.12)	62 (22.22)	142 (50.89)	258 (92.14)	66 (23.57)	163 (58.21)
Fresh Fruit Juice	147 (52.69)	112 (40.14)	28 (10.03)	150 (53.57)	106 (37.85)	39 (13.92)
Soft Drinks	211 (72.63)	132 (47.31)	66 (23.65)	207 (73.92)	127 (45.35)	62 (22.14)
Bakery Products	188 (67.38)	119 (42.65)	57 (20.43)	194 (69.28)	126 (45)	53 (18.92)
Sweets (Mithai)	175 (62.72)	151 (54.12)	23 (8.24)	187 (66.78)	165 (58.92)	21 (7.5)
Fried Snacks	188 (67.38)	133 (47.67)	50 (17.92)	195 (69.64)	146 (52.40)	46 (16.42)
Dried Fruits (Nuts)	46 (16.49)	32 (11.46)	13 (4.65)	35 (12.5)	25 (08.92)	9 (3.21)
Chocolates	72 (25.80)	46 (16.48)	21 (7.52)	72 (25.71)	41 (14.64)	22 (07.85)
Rice (plain)	257 (92.11)	27 (9.67)	186 (66.66)	242 (86.42)	18 (06.42)	182 (65)
Salad	91 (32.62)	9 (3.22)	74 (26.52)	99 (35.35)	14 (05)	80 (28.57)

1-2 s/month = 1 to 2 serving/month, 1-2 s/wk. = 1 to 2 serving/week

Table 6 : Baseline prevalence of depression and anxiety of patients and caregivers.

Variables	PATIENTS (2656)		p	CAREGIVER (559)		p
	IG* (1352) n (%)	NIG β (1304) n (%)		IG* (279) n (%)	NIGβ (280) n (%)	
(PHQ 9) Severity Cutoff Baseline			.26			.09
Mild - (0 – 5)	973 (72)	928 (71.2)		199 (71.3)	221 (78.9)	
Moderate (6 – 10)	248 (18.3)	266 (20.4)		62 (22.2)	43 (15.4)	
Severe (11 – 27)	131 (09.7)	110 (08.4)		18 (06.5)	16 (05.7)	
GAD (7) Severity Cutoff Baseline			.25			.67
Mild - (0 – 5)	1060 (78.4)	993 (76.2)		221 (79.2)	229 (81.8)	
Moderate (6 – 10)	214 (15.8)	238 (18.3)		42 (15.1)	35 (12.5)	
Severe (11 – 21)	78 (05.8)	73 (05.6)		16 (05.7)	16 (05.7)	

* Intervention Group - β Non-Intervention Group - (P value significance level at 0.05)

DISCUSSION:

Our study explored the ability of mobile phone text messages to reduce mortality and cardiovascular risk factors in newly diagnosed cardiac patients and their primary caregivers. The randomized clinical trial resulted in enrolment of patients and their respective caregivers with comparative demographics between the IG population and the NIG

In recent years the advancement of tele media communication technology, especially mobile phone, has enabled medical professionals and other health care providers to exploit its ease of use and widespread availability in health care delivery [103]. Specifically mobile phone text messaging has been shown to promote positive lifestyle modification and disease prevention, including smoking cessation [72, 104, 105], physical activity[106], weight management [107], healthy diet[108], DM management [72, 109, 110], and psychological wellbeing [107, 111].

SIGNIFICANCE of the Study PROTOCOL

In contrast to the ubiquitous availability of well-established cardiac rehabilitation facilities in the developed nations, developing countries such as Pakistan are often devoid of systematic preventative care. Due to lack of appropriate resource and high disease burden, hospital and clinic medical practice focus on the essential, more urgent therapeutic aspects of disease management. The majority of clinical trials on similar objectives have addressed only one or

two cardiovascular risk factors [112-114]. Our clinical trial on other hand, examined the effect of SMS (text messaging) on multiple cardiovascular risk factors, by a unique SMS (text messaging) based positive behavior change intervention to newly diagnosed CAD patients and their care-givers. To our knowledge, our clinical trial is the first in Pakistan to address the post cardiac event health management by SMS (text messaging) for the patients and their care-givers. The role of care givers and consequent adverse effect experienced by taking care of post event cardiac patient are well documented [54, 56]. A well informed care-giver is likely to be less stressed and psychosocially more stable, and more confident in taking care of their patients. This trial is also the first, to our knowledge, which addressed mortality as a primary outcome measure in the study of post cardiac event patient and their care-givers.

BASELINE CHARACTERISTICS of STUDY SUBJECTS

The data from our study confirmed the high prevalence of modifiable risk factors among CVD patients in Pakistan. Majority of the patients were male and married, and nominated their spouse as their care-giver, therefore expectedly, due to cultural trend, the mean age of the female care-givers (wives) were younger than the patients (39 yrs. Vs 52 yrs.). The mean age of our study patients are consistent with recent studies from Pakistan and other SA countries, and was significantly lower than Western countries [99, 115-117] underscoring the more aggressive nature of CVD affecting South Asians, including Pakistani. Our study showed that 41% of the patients and 70% of the caregivers had any formal education, and 30% versus 60% had secondary and higher education, respectively. Previous studies from Pakistan showed 18 % of the cardiac patients and 42.4% of controls had tertiary education [99, 117]. Several studies from South Asia showed a higher CAD burden and prevalence of CVD risk factors among individuals with low levels of education [118-120]. Jaffrey et al [53] studied the cardiovascular health knowledge and behaviors in a large cohort of cardiac patients from tertiary care hospitals. The authors found that while 73% of the patients had primary school education or

higher striking, gaps existed in knowledge, particularly on the nature of CAD, its common symptoms and modifiable risk factors.

PREVALENCE of MODIFIABLE RISK FACTORS

- **Tobacco Smoking**

In our study Tobacco smoker comprised 23% (22.70% of IG and 23.40% of NIG) of the patients the prevalence of tobacco smokers in caregivers was only 9% (9.30% of IG and 8.60% of non-IG). The low prevalence of smokers among the caregivers may be due to gender bias [115]. Prevalence of smoking in the population of different SA countries was reported to be in between 21% and 72%, and around 28% among Pakistani population [121]. Whereas studies done in Pakistan showed that prevalence of smoking was in the range of 37% to 50% [116, 117]. A meta-analysis of 13 studies involving heteronomous population cohorts from developed countries found SMS was overall efficacious in promoting smoking cessation [72, 104].

- **Physical Activity**

In the present study, the baseline data showed, that 41% of patients were doing moderate physical activity for a mean of 5 days per week (almost same distribution in IG and NIG). Fifty-six percent of the caregivers were engaged in moderate physical activities for a mean of 6 days per week (57.3 % in IG and 55% in NIG). Thirty-seven percent of the patients walked on an average of 5.5 days per week, for an average of 38 minutes per day (39% in IG and 35% in NIG). Almost same walking pattern was observed in caregivers, but with a slight longer duration of walking time, on an average of 42 minutes per day. Average sedentary time spend by patients was 405 minutes (almost 7 hrs.) per day, whereas 393 minutes (6.5 hrs.) was spend by caregivers. A study conducted in Karachi Pakistan to find out risk factors for CAD reported that 40% of the study subjects were engaged in regular physical activities [117]. Another study reported 4.3% of their study subjects were doing regular exercise [63]. Data from

INTERHEART study showed that 4.6% of the study subjects from SA countries and 15.8% of study subjects from other countries were engaged in moderate to high intensity physical activities [115]. In comparison with published data from SA countries our study population showed that greater number of individuals were engaged in moderate to vigorous physical activities, which is not consistent with other results. This difference between studies results suggest that in recent years the rapid growth of digital media, and internet may have influenced our study subjects' attitude towards adopting positive lifestyle.

- **Food Frequency**

Present study used food frequency questionnaire based on the local food items. The food choices of patients and their respective caregivers are quite similar due to the fact that they belong to the same family and share the same food, even then patients appeared to have preferences for healthier food. Caregivers appeared to outnumbered patients in consumption of sweets (64% vs 51%). Similar trend observed in potatoes consumption (94% of caregivers, 88% of patients), beef (caregivers 72%, patients 66%), soft drinks (caregivers 75%, patients 68%) ice cream (caregivers 64%, patients 47%), fruits (caregivers 92%, patients 87%), chocolates (caregivers 25%, patients 6%). More than 90% of the study subjects eat vegetables, beans/lentils and chicken, at least once per week. There was no major difference between patients and caregivers in the consumption of goat meat, egg white, salad, fresh fruit juices, bakery product, and plain rice. Studies from Karachi, Pakistan reported that 14% of their study subjects consumed fruits, 32% to 83% consumed red meat, and 37.8% to 72.7% use saturated fat in their cooking [99, 115, 117, 122]. The data from INTERHEART study showed that 20% of CAD patients from SA countries consume fruits and vegetable as compared to 38.3% from other countries, whereas 26.5% of controls from SA and 45.2% from other countries consume fruits and vegetables[115]. Studies done on the relationship of diet and cardiovascular disease report that consumption of potato, red meat, and high intake of sodium was positively

associated with the risk of developing CAD [123-125]. On the other hand, consumption of fruits and vegetables, dairy product, egg, rice, and dark chocolate are inversely related with the risk of CAD [126-132].

- **Depression and Anxiety**

Results from our study is consistent with data published from Pakistan and elsewhere [45, 133-135]. Our study implemented validated Urdu version of Patient Health Questionnaire (PHQ9) to evaluate depression, and Generalized Anxiety Disorder (GAD7) scale to evaluate baseline anxiety. PHQ9 and GAD7 have been used to evaluate depression and anxiety among CAD patients, and it has been validated in diverse cultural background [136-138]. The results of this study showed that 28.42% of the patients had moderate to severe depression (IG 28%, NIG 29%) at baseline assessment. Anxiety was present in 22.70% of patients (IG 22%, NIG 24%). Whereas, among caregivers' depression was acknowledged by approximately 25% of the participants (IG 29%, NIG 21%), and around 20% suffered from anxiety (IG 21%, NIG 25%). Study conducted in Saudi Arabian population showed that 31% patients visiting primary health care had mild and 13.4% had moderate depression [138]. Results from our study are in accord with previous studies indicating that prevalence of depression in CAD patients in Pakistan was reported to be in range of 27% to 37% [139, 140]. A clinical trial on three months effect of mobile internet based cognitive therapy on the course of depressive symptoms in remitted recurrently depressed patients reported that internet and text messages based cognitive therapy in patients with remission of depression is effective, however, it's long term effectiveness and replication to be evaluated further [141]. Systematic review of 13 studies, mostly pilot studies with small sample, concluded that SMS text messaging may be an effective intervention for persons suffering from depression [142]. The authors indicated that larger randomized clinical trials are needed before recommendation can be done for implementation of specific depression SMS text messaging IG in primary care [142].

The present study showed that 33% of study patients, and 12% of caregivers had DM. HTN was prevalent in 56% of the patients and 31% of the caregivers. Studies done in Pakistan showed prevalence of DM from 22% to 30% in CAD patients [116, 117]. Analysis of INTERHEART study showed that 20.2% of the CAD patients and 9.5% of non-CAD subjects in SA countries had DM, and in comparison 18.2% of patients and 7.2% of their controls from other countries suffer from DM [115]. Study conducted in Pakistan to explore knowledge of CAD risk factors in CAD patients reported, that HTN was present in 43% of their study subjects [63]. WHO report on chronic diseases showed that prevalence of HTN was reported to be in the range of 30% to 40% in SA countries. Result from our study showed consistent results for the presence of DM, but HTN appeared to be more prevalent as compared to the previous local and regional data. High prevalence of HTN in Pakistani population may indicate that there may be not an effective preventive strategy or present strategies are not working. New effective strategies are to be explored to reduce the burden of HTN and DM.

STRENGTH and LIMITATIONS:

To our knowledge this is the first study utilizing mobile phone text messages for health education in Pakistan, with fairly large sample size, and included primary care-givers as study participants along with their respective CAD patient. Limitations to be consider are, biochemical risk factors were available in a small sample of the study population, due to resource constraint and logistical difficulties. Only 21% of the caregivers, nominated by their respective patients, consented to participate in the study, whereas 79% refused to participate. The main reason for refusal was that they were not comfortable for a follow-up commitment. Various factors influence the relatively low rate of follow-up, including relative lack of patient compliance to travel, absence of material incentives or inducement, frequent safety and security concerns. Other factors, including ethnicity, level of education may also play a role. The study

may also have an element of recall bias, as subjects may have responded positively to all risk factors introduced, knowing that the study was about heart disease and risk factors [63]

CONCLUSION

We designed a prospective, randomized controlled, single blinded clinical trial in Pakistan to study the benefits of SMS targeting major modifiable risk factors associated with CAD. A novel approach was used to address the "Caregiver Strain" by recruiting caregivers as a parallel group along with their respective CAD patients. Results of the trial should assist in understanding the prognostic benefits of SMS among CAD patients and their care givers.

Competing interest:

No competing interest was declared by the authors.

Trial Registration:

The clinical trial is registered at Australia New Zealand Clinical Trial Registry (Reg. No: ACTRN12611000388910.)

Funding/Support:

The study was funded by a research grant from the Cardiac Health Institute, Sydney. Pathology studies were partially subsidized by Essa Diagnostic Laboratory, Pakistan

AUTHORS' CONTRIBUTION

Study Concept and Design:	Ismail
Protocol development and review:	Ismail, Kiat, Strodl, Ansari, Jun Ma,
Macquarie University Ethics application:	Ismail, Kiat
Study sites approval & IRB:	Ismail, Kiat
Data collection and management:	Ismail
Drafting of the manuscript:	Ismail
Critical revision of the manuscript:	All authors
Statistical analysis:	Ismail, Strodl, Jun Ma
Obtained funding:	Kiat
Administrative, technical, or material support:	Ismail, Kiat, Ansari
Study Supervision:	Ismail, Kiat

ACKNOWLEDGMENT

We are thankful to all study participants to consent in the study and shared their experiences throughout the trial, as without their cooperation we would not have be able to get insight for our objectives. We acknowledge the contribution of our research assistants, Ms. Mehreen Aziz, Ms. Javeria Saeed, Ms. Yusra Iqbal, Ms. Safia, and Ms. in collecting the data for the study. We are grateful for Essa Diagnostic Laboratory for providing the laboratory investigations on discounted rates. We appreciate the cooperation of all our participating study sites.

CHAPTER 3:

Mobile phone-assisted psychological wellbeing for the prevention of coronary heart disease – randomized controlled clinical trial

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Title:

Mobile phone-assisted psychological wellbeing for the prevention of coronary heart disease – randomized controlled clinical trial

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Key Words:

Cardiovascular disease	(CVD)
Coronary Artery Disease	(CAD)
Diabetes Mellitus	(DM)
Disability-Adjusted Life-Years	(DALYs)
Electro Cardio-Gram	(ECG)
Generalized Anxiety Disorder	(GAD)
Hypertension	(HTN)
Karachi Institute of Heart Diseases	(KIHD)
Mobile Health	(mHealth)
Multimedia Message service	(MMS)
Myocardial Infarction	(MI)
National Institute of Cardiovascular Diseases	(NICVD)
Non Communicable Diseases	(NCD)
Patients Health Questionnaire	(PHQ)
Randomized Clinical Trial	(RCT)
Research Assistant	(RA)
Short Message Service	(SMS)
South Asian	(SA)
Tabba Heart Institute	(THI)
Usual care and Intervention group	(IG)
Usual care and non-intervention group	(UCG)
World Health Organization	(WHO)

Mobile phone-assisted psychological wellbeing for the prevention of coronary heart disease – randomized controlled clinical trial

ABSTRACT:

Background:

Psychological factors, like depression and anxiety, are among the major contributing modifiable risk factors for the development of coronary artery disease (CAD).

Text messaging may be a preventive tool in reducing psychological distress among CHD patients and healthy care givers. This study aimed to explore the effectiveness of a text messaging intervention for improving the mental and physical health of patients with CHD.

Methods:

A randomized, single blinded, clinical trial was conducted in 3 cardiac specific tertiary care hospitals in Karachi, Pakistan. Participants were patients who had their first cardiac events and their respective nominated care-givers. Patients and their care-givers were randomized into two groups, intervention (IG) or usual care group without intervention (NIG). Research assistants, recruiting the subjects were blinded to the IG or NIG. Validated Urdu version of PHQ9 and GAD7 was implemented at baseline and at every subsequent follow-up. Positive psychological wellbeing motivational text messages were sent twice weekly to the intervention group.

Results:

Analysis revealed that motivational psychological wellbeing SMS messages through mobile phone does not have any significant effect in reducing depression and anxiety among intervention group as compared to non-intervention group. Although female participants were more depressed and anxious than male participants in both group, there were no gender differences in the outcome of the intervention.

Conclusions:

SMS text messaging alone was not effective in improving the psychological wellbeing of Pakistani adults with CAD. Future studies with such populations should explore augmenting long term mobile phone text messaging with brief face-to-face counselling sessions.

Key words: coronary artery diseases, caregivers, short message service, text messages, intervention, clinical trial, depression, anxiety, psychological wellbeing.

TITLE:

Mobile phone-assisted psychological wellbeing for the prevention of coronary heart disease – randomized controlled clinical trial

SHORT TITLE: TEXT-2B-HAPPY

INTRODUCTION:

Cardiovascular disease (CVD) including, coronary artery disease (CAD) and cerebrovascular disease killed 17.5 million people globally in 2012[1, 2]. Three-quarters of global deaths due to CAD occurred in low and middle income countries, the majority of which were considered premature deaths (under the age of 70 years) [1-5]. Epidemiological studies in migrants of South Asian (SA) origin (i.e. from India, Pakistan and Bangladesh) living in the high income/developed world countries have consistently demonstrated disproportionately high incidences of CAD related mortality [7, 8, 11, 17, 26, 81-90]. In Pakistan CAD is a major public health problem [91-93], impacting on the nation's economy by disabling a significant proportion of the working age population.

The World Health Organization (WHO) identified four major preventable behavioral risk factors for CAD that are largely related to 21st century lifestyle: tobacco use, unhealthy diet, insufficient physical activity, and harmful use of alcohol[5]. American Heart Association recognized depression as an official risk factor for cardiac disease [143]. Depression is usually co-morbid with anxiety in CAD patients [144].

At least 80% of premature deaths from heart disease can be avoided by engaging in healthy lifestyle [30]. In the last couple of decades, a sleuth of studies identified depression, anxiety and other psychosocial factors including nonphysical stress as potent risk factors for CAD, associated with an increased risk of mortality [32-36]. Psychosocial risk factors (PSRFs), like depression and anxiety, are not only associated with the incidence of CAD, but it also

contributes in low-health related quality of life, recurrent cardiac events, CAD related and all-cause mortality, and poor prognosis in established CAD patients [36, 37]. Being a patient of CAD and having a lifelong treatment increases the level of depression and anxiety, which gradually instill the fear of dying and helplessness [37]. That fear of death and helplessness may negatively affect the prognosis after CAD [37]. Studies done on CAD patients with depression and anxiety showed that presence of depression and anxiety may affect behaviours change such as, smoking, dietary preferences, physical activity, which in turn can influence the risk of CAD [38]. CAD patients with depression tend to have unhealthier diets, smoke more, engage in less physical activity, are less likely to seek medical care, and have poorer adherence to medical regimen [39, 40]. As such mental health conditions such as depression are important targets for intervention in CAD patients.

The literature is replete with research outcomes on patient-centered care, but little information is available on patients' informal caregivers. Family caregiving is defined as extensive care to the patients, without any financial benefits, by spouses, parents, and loved ones [51]. Caregivers are usually involved in direct assistances (e.g., helping in daily activities, medication, and lifestyle management), monitoring symptoms, maintaining physician appointment and accompanying at physician clinic[51]. All these additional workloads put caregiver at "caregiver strain", which causes sleep disturbance, physical exhaustion, changes in their personal plan, depression, and anxiety [52-55]. Family caregivers has an important role and it has been recognized, that the high physical and psychosocial demand exposes them to a greater risk of ill health including a greater risk of mortality due to CVD [54, 56]. Intervention has been recommended for the wellbeing of the caregiver [57], but, to our knowledge none has been developed and implemented in countries such as Pakistan.

With the rapid advancement in tele-media access, new technologies are providing promising methods of delivering more cost effective and efficiently deliver health care [64].

One such promising method of health care delivery is the use of mobile phone technology, referred as mHealth [65] which include text messaging, video messaging, video calling, and internet connectivity [66, 67]. Mobile phone text messaging in particular has a great potential as a tool for public health care interventions. It is easy to execute, low cost, and the service is available in all contemporary mobile phones. Short text messages (SMS) widespread use, its ability to present succinct and instantaneous yet durable information makes text messaging suitable for a wide variety of health care management measures [66, 68]. Advantages of text messaging also include ready access of information when and where ever convenient to the patients [66], reliability of delivery (even if the phone is turned off when the message is delivered the patient will still receive it upon turning the phone on) [69]. Text messaging is particularly suitable for behavioral interventions because it allows for in-the-moment, personally tailored health communication and reinforcement. Recent studies have found that periodic prompts and reminders are effective methods to encourage and reinforce healthy behaviors [70, 71].

The number of mobile phone users in Pakistan reached 136.5 million mark at the end of March 2014, and this number continues to grow at a fast pace [77-79]. In 2011, the number of text messages exchanged in Pakistan jumped to 238 billion from 152 billion in 2010, illustrating the upwards trend in SMS usage [80]. Importantly, mobile phones also have huge penetration in rural areas of Pakistan. As a result, mHealth has the potential to deliver healthcare programs to the entire population of Pakistan.

Despite the high prevalence of depression and anxiety and associated poor outcomes in CAD patients such mental health conditions are generally not properly recognized and managed [75, 145]. Psychological support for CAD patients was recommended to be part of every cardiac rehabilitation program [37]. One of the goals of cardiac rehabilitation is to identify cardiac patients with depression and anxiety and then offer intervention for

psychological support to reduce cardiovascular risk, improve health related quality of life (HRQoL) and facilitate the patient return to regular family, social and work related life [37]. The traditional rehabilitation programs are delivered face-to-face in specialized hospital based settings; however, they are poorly attended, mainly due to poor accessibility and access[146]. The lack of attendance in cardiac rehabilitation programs are further limited in CAD patients with depressive symptoms of helplessness and hopelessness[73]. Innovative approaches are needed to overcome limitations related to those secondary prevention program for CAD patients with depressive symptoms.

Recent studies have concluded that mHealth based approaches to deliver preventive programs may overcome many of the barriers to participation in traditional rehabilitation programs, and they are effective in improving behavioral and clinical outcomes for CAD patients and in patients of CAD with depression and anxiety[73, 75]. Studies were conducted with the aims to manage depression as well as CAD risk factors behaviours using telephone-based care management model [73, 74] incorporating Cognitive Behavior Therapy (CBT) counselling [73, 75]. The intervention comprises of telephonic session of CBT counselling, goal setting and motivational interviewing technique [73]. Study done in USA explored a mobile phone context aware system that can sense a person behavior and then provide a treatment platform that can positively reinforce adaptive behavior and provide support for changing those that contribute to depression [76]. The study was conducted on 8 participants and it showed promising results. Although, telephonic CBT session as an intervention was effective as compared to the usual care, but it's requirements to implement, like, trained master level psychologist, cost of at least 30 minutes cellular/landline voice time, physical resources allocated to establish the specific mechanism, and the ambiguity regarding the economic effect of the intervention, make it difficult to implement in countries where budget allocated for health care is not even enough to provide basic health provisions [75] .

According to Pakistan economic survey 2014-15, government spent 0.42 percent of gross domestic product (GDP) on health and nutrition [147]. However, the percentage spent on health is way below those recommended by the WHO. It is estimated that US$ 34 per capita is required for a package of essential health services in Pakistan; however, the total expenditure on health in Pakistan is US $ 18 per capita out of which the total government health expenditure is only US$ 4 per capita [148]. Reviews of the Pakistan health care system indicate that it is inadequate and expensive, with an underfunded and inefficient public sector along with highly expensive and unregulated private sector [148]. The poor in Pakistan lack access to secondary and tertiary health care systems [149]. In addition, the high cost of depression keeps a vast majority of the population away from ongoing treatment which contributes to the misery of the illness and associated loss of productivity [150].

In Pakistan, where there is a high prevalence of CAD [26], and the associated PSRFs contribute significantly in adverse CAD consequences that include worse health-related quality of life (HRQOL), impaired functional status, recurrent cardiac events, and higher rates of mortality [134]. Low funded, resource constraint, inefficient and inadequate health care system of Pakistan have less room for efficient, affordable and far reaching face to face cardiac rehabilitation programs including CBT sessions, even on telephone. Whatever few cardiac rehabilitation facilities exists in private sector hospitals in Pakistan, they are attended by very few patients [151]. The vast majority of Pakistani population cannot benefit from secondary or tertiary health care system (public and private) due to inaccessibility, unaffordability, and lack of trained human and modern physical resources [148]. This is unfortunate given that the majority of the population lacks substantive knowledge on risk reduction related life style modification measures [62, 63]. Effective, efficient, acceptable, affordable and easily accessible educational/cardiac rehabilitation strategies are greatly in need, especially in resource constraint countries like Pakistan. The effectiveness of utilizing SMS (text messaging)

for psychological wellbeing program in combination of CAD modifiable risk factors management program is yet to be established. The outcome of such program could not only benefits psychological wellbeing to improve all aspects of HRQOL, but also CAD risk factors. The intervention program could also show economic benefits over more traditional mode of delivery. We therefore undertook a novel approach to utilize a mHealth program for patients who had sustained nonfatal cardiac events and also include their primary care givers in Pakistan. The aim of our clinical trial was to find out the effectiveness of text messages (SMS) as an intervention to provide psychological support in reducing depression and anxiety in cardiac patients and their care-givers.

METHODOLOGY:

Trial Design

The study was designed as a randomized, controlled, clinical trial. The subjects were randomized with an almost equal ratio in intervention and non-intervention group.

Ethical Considerations

Ethics approval for the study was granted by the Human Ethics Review Board of Macquarie University. Approvals were also obtained from the institutional review boards of each participating hospital. A detailed consent form was developed for the patients explaining the objectives of the study and their rights. The informed consent form was drafted in English, translated into Urdu by certified translators, then back into English to ensure accuracy. At enrollment, participants were asked to read the informed consent form and encouraged to ask questions for clarification and were told that their participation was voluntary and that they could withdraw at any time during the course of the study.

Participants

Study Participants

The first group of participants comprised cardiac patients who had suffered their first *non-fatal* cardiac event related to CAD, and admitted in one of our participatory study hospitals. The second group of study participants consisted of primary care-givers, nominated by their respective cardiac patients. Primary care giver designated by the patients was defined as a spouse, adult child or parents of the patient, mainly responsible for daily care of their patients [51].

Eligibility Criteria

Participants were recruited if they were in a sound state of mind (i.e. no self-reported symptoms of psychosis, delirium, and dementia), and were able to communicate in a coherent way, willing to participate in the study, had stable cardiac status at discharge, owned a personal mobile phone with a personal subscriber identification module (SIM), were willing to retain

the same SIM during the study period (or were willing to inform the investigators if their phone number changed), understood the basic operations of a mobile phone, were able to read text messages, and did not have any significant life-threatening co-morbidities (such as terminal cancer or end stage renal disease). Participants were excluded if they did not own a mobile phone and were unwilling to acquire one, were pregnant females, or were below the age of 18 years.

Study Sites

The study was conducted at three tertiary care cardiac specific hospitals with basic and advanced facilities for cardiac care in Karachi: National Institute of Cardiovascular Diseases (NICVD), Karachi Institute of Heart Diseases (KIHD), and Tabba Heart Institute (THI). The majority population of Karachi falls into the catchment of these three cardiac hospitals.

Intervention

All consenting participants were assessed for depression and anxiety prior to leaving hospital using the Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorder Scale (GAD-7). The intervention commenced within two weeks of baseline assessment and is delivered by one of study investigators, Dr. Javed Ismail (JI). The intervention aimed to manage depression and anxiety as well as CAD risk factors behaviours using SMS text based behaviours change messages.

Mobile phones were used to deliver positive behavioral change/lifestyle modification health messages to the intervention group by SMS. These messages were specifically designed to be culturally sensitive in order to be phrased in ways that would be acceptable to a Pakistani population. The primary (for care-givers) and secondary prevention (for patients) programs for CAD were based on guidelines developed by WHO and the National Heart Foundation of Australia [32, 33, 96]. The pool of health messages was developed by the study investigators.

The messages were pilot tested in 300 subjects and assessed for their level of comprehensibility and comfort. Messages that were not easily understood were re-worded to eliminate ambiguity. Some of the messages sent to the IG in lay language (and translated into English) are as follows;

- Small steps towards healthy life, will one day make a big change in your life
- Daily walk will reduce your depression, and blood pressure.
- A calm and strong person can convert losses into profit.
- Go out with your family for a picnic or dine, at least once in a week.
- Don't sit idle, keep yourself busy in doing good deeds.
- Enjoy life, and find consolations with those that are worse off than you.
- Smoking tobacco is injurious to your health, especially for heart.
- Be physically active (at least 30 minutes on most week days);
- Make healthy food choices;
- Increase vegetable intake; they are a healthy source of vitamins, minerals & fiber.

Messages were also sent to subjects in the IG to remind them of their appointment schedule and to adhere to their prescribed medications. Messages were limited to 160 characters and were phrased in a layman terminology. During the initial 3 months following enrollment, 2 messages were delivered every week. After 3 months, the frequencies of messages were increased from 2 to 6 messages per week. In contrast, the NIG received general greeting messages, (e.g. thanking them for being in the study), and reminders about their follow-up appointments. Those messages were sent out fortnightly.

Baseline Data Collection

The study data were collected from June 2012 to December 2013 from three participating cardiac specific hospitals. Baseline clinical and anthropometric data were collected at the time of participant's initial contact in hospital. Both, patients and caregivers were approached by a research study assistant. Patients and caregivers were interviewed separately, and were

instructed not to exchange information with each other during the interview. Patients' and caregivers' demographic, cigarette smoking history, use of smokeless tobacco, physical activity, leisure time physical activity, dietary habits (especially consumption of dietary fat), anthropometric measurements, co-morbidities (including HTN, DM, angina pectoris), family history of CAD, depression, anxiety, and body mass index (BMI), were collected through a standardized questionnaire. Information about current diagnosis, medical history, treatment data and prescribed medication data were extracted from patient's hospital medical records. Current state of depression was assessed through use of 9-item Urdu version of patient health questionnaire (PHQ-9), and 7-item Urdu version of generalized anxiety disorder (GAD-7) [102]. An experienced laboratory technician drew venous blood samples from subjects following a 12-hour overnight fast. The blood samples were sent to the laboratory (Dr. Essa's Laboratory and diagnostic center, Karachi, Pakistan) for lipid profile and HbA1c.

PHQ-9, and GAD-7 are based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for major depressive, and generalized anxiety disorders [152, 153], with excellent reliability and validity, as well as criterion, construct, factorial, and procedural validity[154]. PHQ-9 is a standardized and reliable scale that has been implemented extensively among cardiac patients [155, 156]. PHQ nine items assess the frequency of depressive symptoms experienced in the past 2 weeks. Each item is scored on a 4-point Likert scale with response rated from 0 (not at all) to 3 (nearly every day) with a sum score between 0 and 27 points, which is derived by adding all nine items. Symptoms of depression are graded as; up to 4 (absence of depressive symptoms); scores of 5 to 9 (mild); scores of 10 – 14 (moderate); and score of 15 and higher represent severe depression [157]. It is recommended that a PHQ-9 score of $\geq$ 10 is a valid single screening cut-off that has 88% sensitivity and specificity to detect a major depressive disorder[152]. GAD seven items assess the frequency

of main symptoms of generalized anxiety within the past 2 weeks, and items are scored similarly as PHQ with a sum score ranging from 0 to 21 [158].

Validity (Internal consistencies)

The PHQ-9 and GAD-7 has been reported as valid and reliable, and has been frequently used in CAD patients [152, 159-161]. The Cronbach's alpha coefficient for the internal consistencies for the PHQ-9 was documented from 0.84 to 0.90, whereas for GAD-7 it was reported as 0.79 [154, 162]. In our study, the Cronbach alpha coefficient for PHQ9 was 0.82, and for GAD7 Cronbach alpha coefficient was 0.79.

Data derived from and collected for this study were not made available to the patients' physicians.

Follow-Up Data Collection

The first follow-up was made on an average of six months (range: 180 days – 400 days) following enrolment. Subsequent 2 follow-ups occurred at 90 days' intervals. Questionnaire containing PHQ-9 and GAD-7 was administered at baseline and at follow-ups, laboratory investigations for blood tests were performed at baseline assessment and at first follow-up, until funds for laboratory investigations last. The communication in between follow ups was of a two-way nature. Participants were encouraged to send general enquiries about major risk factors by SMS. Javed Ismail (JI) responded to their queries within 48 hours. Voice calls were also responded to where possible. Via SMS queries from the IG were answered in detail, whereas lifestyle modifications related queries from the NIG were not answered specifically. Instead, they were advised to consult their treating physician. Members from either group with queries relating to specific health conditions including medications and symptoms were directed to their treating physicians. The study was not designed to evaluate the pharmacologic therapies administered to the patients by their treating physicians and did not interfere with

their routine medical care. Information derived from this study was not made available to the treating health care professionals of the participants

Outcomes

The two primary outcomes measure were changes in depression and anxiety scores which were assessed using PHQ-9 and GAD-7, respectively.

Sample Size

The sample size was calculated on the basis of the dichotomous outcome variables (depression and anxiety). Previous studies have shown that prevalence of depression and anxiety in general population and CAD patients in Pakistan, range from 06% to 53% [163, 164]. The sample size was calculated based on an average prevalence of anxiety and depression of 15% among general and CAD patients, with 80% power, 5% significance level, and 10% difference (from 15% to 5%) in the reduction of depressive and anxiety between groups, the calculated sample size was 700 patients in each group. After assuming a 10% attrition rate, the final sample size was determined as 770 patients in each group (1540 total). With a patient and caregiver ratio of 1:1 the total sample size deemed appropriate was 3080 with 1540 participants each for patients and caregivers.

Randomization

Patients were randomly assigned to the *intervention group* (IG) or the Non-intervention/ *usual care group* (NIG). A randomization list of 100 subjects for each site was generated with a block size of 8 in STaTa software, and almost equal proportions of participants were randomized in the IG and NIG. The subjects were randomized by their study registration number. The list was kept with one of the investigators Javed Ismail (JI) who supervised the data collection but did not have direct personal contact with the subjects at the time of baseline recruitment. RAs gave subjects a consecutive study registration number, and sent their questionnaires with the allotted study registration number to the study office. JI than assigned

a group, IG or NIG, to each patient as per the randomization list. The delivery of behavioral change SMS text messages, and replies to the queries of the study subjects were done by JI. Participants were asked not to reveal the group to which they have been randomized when completing data assessments at follow-up. Research assistants who were collecting the data were blinded to participants' group allocation, whereas JI was blinded to the baseline health profile of the participants at the time of allocating randomization group.

Statistical Analysis

Intention to treat was the primary approach for the analysis. Allowances were made for attrition in the sample size estimation but analyses were performed on the data with and without missing values. Where possible, data were collected as continuous variables. Continuous variables were converted to categorical variables during the analysis phase where necessary. A descriptive analysis was performed to examine the socio-demographic characteristics of the study population. Student's t test, Chi square and Fisher's exact tests were conducted to determine the homogeneity of demographic and clinical characteristics of the IG and NIG. A one-way repeated measure ANOVA was conducted to compare scores on depression (PHQ9) and anxiety (GAD7) with intervention at baseline assessment and subsequent follow ups. A mixed between-within subjects' analysis of variance was conducted to assess the impact of intervention on participants' scores on depression and anxiety across baseline assessment and subsequent follow-ups. A one-way between groups multivariate analysis of variance (MANOVA) was performed to compare the mean score difference of an independent variable on the combined dependent variables. Two dependent variables were: depression (PHQ9) and anxiety (GAD7). Preliminary assumptions were checked, with no serious violation noted. . The data was analyzed using IBM® SPSS® statistics software (V 21, IBM Corporation, U.S.A)

RESULTS:

A total of 2656 patients and 559 caregivers were enrolled, between June 2012 to December 2013. Mean first follow-up period was 154 days (± SD 100), second follow-up period was 273 days (± SD 89) from baseline assessment, and 3rd follow-up period was 329 days (± SD 70) from baseline assessment. Patients and care-givers participation and their breakdown is illustrated in figure 1.

Baseline Socio-demographic characteristics and major risk factors attributable to CAD

Demographic and baseline characteristics were similar between the intervention and the non-intervention groups, in patients and caregivers. Majority of patients from all participating sites were male, while female represented the larger proportion among caregivers (approximately 65%), large proportion of subjects were married, and more care givers had formal education. Between groups (IG and UCG/NIG) there were no difference in prevalence of risk factors among patient and care-givers. Majority of patients smoked, IG (23%) and UCG/NIG (23.40%), p = 0.25 than caregivers, IG (09.30%) and UCG/NIG (09%), p = 0.35. Similar situation exists for the prevalence of DM and HTN (see table 1).

Table 1: Baseline Socio-Demographic characteristics of patients and care givers

Variables	PATIENTS (2656)		p	CAREGIVER (559)		p
	IG* (1352) n (%)	NIG$^{\beta}$ (1304) n (%)		IG* (279) n (%)	NIG$^{\beta}$ (280) n (%)	
Gender			.35			.10
Male	892 (66.0)	838 (64.3)		95 (34.1)	114 (40.7)	
Female	460 (34.0)	466 (35.7)		184 (65.9)	166 (59.3)	
Age (Yrs.)						
Mean (± SD)	52.3 (10.3)	52.2 (10.3)	.73	39 (11)	39.2 (11.3)	.83
Marital Status			.54			.48
Married	1315 (97.3)	1272 (97.5)		236 (84.60)	225 (80.40)	
Unmarried	13 (01.0)	15 (01.20)		37 (13.30)	45 (16.10)	
Divorced/widowed/ separated	09 (0.70)	09 (0.70)		02 (0.70)	05 (1.80)	
Formal Education	558 (43.50)	532 (40.80)	.35	199 (71.30)	188 (67.10)	.49
Employment	620 (45.90)	589 (45.20)	.30	117 (41.90)	119 (42.50)	.19

*** Intervention Group, $^{\beta}$ Non-Intervention Group (p value at a significance level of .05)**

Table 1a: Baseline prevalence of major CAD Risk factors of patients and caregivers

Variables	PATIENTS (2656)		p	CAREGIVER (559)		p
	IG* (1352) n …(%)	NIGᵝ (1304) n (%)		IG* (279) n (%)	NIGᵝ (280) n (%)	
Diabetes Mellitus	450 (33.40)	429 (33.10)	.86	38 (13.70)	35 (12.60)	.70
Hypertension	764 (56.5)	741 (56.80)	.98	89 (32)	89 (31.80)	.13
Smoking tobacco (cig.)	307 (22.70)	305 (23.40)	.25	26 (09.30)	24 (08.60)	.35
Duration of Smoking Years - Mean - (± SD)	23.6 (±12.7)	22.8 (±13.2)	.81	12.6 (±11.1)	15.3 (±11.3)	.39
Quantity of Cigarette/day Mean - (±SD)	16.8 (±12.5)	15.6 ±10.9)	.19	10.8 (±6.1)	12.5 (±6.8)	.35
Systolic Blood Pressure Mean - (± SD)	128 (±23.38)	128 (±24.02)	.88	138 (±27)	130 (±31.7)	
Diastolic Blood Pressure Mean - (± SD)	77.8 (±13.4)	78.5 (±13.9)	.21	76.6 (±10.5)	76.6 (±10.5)	.58

*** Intervention Group, ᵝ Non-Intervention Group (p value at a significance level of .05)**

Baseline prevalence of depression and anxiety

Patients and caregivers (in both IG and NIG) showed similar findings for depression and anxiety on baseline assessment. PHQ 9 showed that 71.5% of patients (IG + NIG) and 75% of care-givers (IG + NIG) were mildly depressed while 28% vs 25%, respectively, reported moderate to severe depression. Similar trends were observed for anxiety (see table 2).

Table 2: Prevalence of severity of depression and anxiety in intervention and non-intervention participants of patients and care-givers groups.

PATIENTS				CARE-GIVERS		
Variables	**IG*** **n (%)**	**NIG$^{\beta}$** **n (%)**	**p**	**IG*** **n (%)**	**NIG$^{\beta}$** **n (%)**	**p**
Baseline - Depression			.27	***Baseline - Depression***		.20
No Depression	860 (63.6)	819 (62.8)		176 (63.1)	200 (71.4)	
Mild	334 (24.7)	353 (27)		079 (28.3)	059 (21.1)	
Moderate	088 (6.5)	082 (6.3)		015 (5.4)	013 (4.6)	
Severe	070 (5.2)	051 (3.9)		009 (3.2)	008 (2.9)	
1st Follow-up - Depression			.63	***1st Follow-up - Depression***		.40
No Depression	585 (71.8)	587 (72.6)		107 (64.8)	124 (72.1)	
Mild	181 (22.2)	163 (20.2)		043 (26.1)	039 (22.7)	
Moderate	039 (4.8)	047 (5.8)		009 (5.5)	006 (3.5)	
Severe	10 (1.2)	011 (1.4)		006 (3.6)	003 (1.7)	
2nd Follow-up - Depression			.46	***2nd Follow-up - Depression***		.20
No Depression	053 (71.6)	041 (67.2)		019 (59.4)	028 (80)	
Mild	015 (20.3)	015 (24.6)		010 (31.3)	006 (17.1)	
Moderate	005 (6.8)	002 (3.3)		002 (6.3)	0 (0)	
Severe	001 (1.4)	003 (4.9)		001 (3.1)	001 (2.9)	
Baseline - Anxiety			.72	***Baseline - Anxiety***		.05
No Anxiety	961 (71.1)	911 (69.8)		200 (71.7)	219 (78.2)	
Mild	286 (21.2)	299 (23)		062 (22.2)	043 (15.4)	
Moderate	073 (5.4)	067 (5.1)		008 (2.9)	014 (5.0)	
Severe	032 (2.4)	028 (2.1)		009 (3.2)	004 (1.4)	
1st Follow-up - Anxiety			.96	***1st Follow-up - Anxiety***		.11
No Anxiety	632 (77.5)	618 (76.5)		104 (63)	122 (71)	
Mild	145 (17.8)	152 (18.8)		046 (28)	039 (22.7)	
Moderate	032 (3.9)	032 (04)		014 (8.5)	007 (4.1)	
Severe	006 (0.7)	006 (0.7)		001 (0.6)	004 (2.3)	
2nd Follow-up - Anxiety			.99	***2nd Follow-up- Anxiety***		.18
No Anxiety	053 (71.6)	043 (70.5)		020 (62.5)	026 (74.3)	
Mild	015 (20.3)	013 (21.3)		007 (22)	008 (23)	
Moderate	004 (5.4)	003 (4.9)		005 (15.6)	001 (3)	
Severe	0 (0)	02 (3.3)		0 (0)	0 (0)	

*** Intervention Group, $^{\beta}$ Non-Intervention Group (p value at a significance level of .05)**

Changes in depression and anxiety in Patients

The Pearson correlation coefficient for depression (measured by PHQ9) and anxiety (measured by GAD7) shows statistically significant positive correlation between the two variables, r = .663, n = 3215, p = .001 (two tailed). The same trend was observed among intervention and non-intervention groups and among male and female. An analysis of variance

was performed to investigate the effectiveness of our study's intervention in psychological wellbeing.

The multivariate analysis of variance (MANOVA) showed that there was no statistically significant difference between intervention and non-intervention groups on the combined effect of depression and anxiety at baseline (p = .95), 1st follow-up (p = .93) and 2nd follow (p = .745) (see table 3a).

A one way repeated measure ANOVA shows that there was a significant effect for time, from baseline assessment to 1st follow up, on the PHQ9 scores (depression) and GAD7 scores (anxiety) (p = .001 and p = .001 respectively), in patients of intervention group. The effect for time on depression and anxiety was also significant (p =.001 and p = .001 respectively), in patients of non-intervention group (refer table 2a). A mixed between within subject ANOVA shows that there was a substantial main effect for time (p =.001), with both groups showing a reduction in PHQ9 and GAD7 scores across the two time periods. The main effect comparing the intervention between groups was not significant, p = .813 for depression and p = 0.970 for anxiety, suggesting that intervention was not effective in reducing depression and anxiety in intervention group than non-intervention group (refer table 4)

Table 3a: Patients: Multivariate Analysis of Variance (MANOVA): mean difference between intervention and non-intervention groups of patients on the combination of depression and anxiety.

Variable	n	Intervention	n	Non-Intervention	Between Subject Effect (P)	Effect Size (Partial eta sq.)	Wilks Lambda (P)
		M* (± SD)		M* (± SD)			
PHQ9 – Base	1352	4.30 (4.25)	1305	4.25 (4.24)	0.765	0.001	.954
GAD7 – Base		3.77 (3.62)		3.73 (3.48)	0.798	0.001	
PHQ9 – FU1	815	3.13 (3.44)	808	3.18 (3.70)	0.760	0.001	.937
GAD7 – FU1		3.09 (3.00)		3.10 (3.01)	0.956	0.001	
PHQ9 – FU2	74	3.18 (3.66)	61	3.67 (3.99)	0.453	0.004	.745
GAD7 – FU2		3.43 (3.48)		3.67 (3.70)	0.700	0.001	

M = mean, SD = standard Deviation, PHQ9- Base = PHQ9 score at baseline, PHQ9-FU1 = PHQ9 scores at first follow-up, PHQ9-FU2 = PHQ9 scores at 2nd follow-up, GAD7- Base = GAD7 score at baseline, GAD7-FU1 = GAD7 scores at first follow-up, GAD7-FU2 = GAD7 scores at 2nd follow-up.

Table 3b: Care-Givers: Multivariate Analysis of Variance (MANOVA): mean difference between intervention and non-intervention groups of care-givers on the combination of depression and anxiety.

Variable	n	Intervention	n	Non-Intervention	Between Subject Effect (P)	Effect Size (Partial eta sq.)	Wilks Lambda (P)
		M* (± SD)		M* (± SD)			
PHQ9 – Base	279	4.01 (4.25)	280	3.36 (3.95)	0.060	0.006	.142
GAD7 – Base		3.49 (3.98)		2.95 (3.59)	0.094	0.005	
PHQ9 – FU1	165	4.04 (4.31)	172	3.26 (3.59)	0.072	0.010	.012
GAD7 – FU1		3.85 (3.72)		3.67 (3.71)	0.657	0.001	
PHQ9 – FU2	32	4.31 (4.18)	35	2.60 (3.35)	0.068	0.004	.091
GAD7 – FU2		4.47(4.01)		2.26 (3.07)	0.013	0.001	

M = mean, SD = standard Deviation, PHQ9- Base = PHQ9 score at baseline, PHQ9-FU1 = PHQ9 scores at first follow-up, PHQ9-FU2 = PHQ9 scores at 2nd follow-up, GAD7- Base = GAD7 score at baseline, GAD7-FU1 = GAD7 scores at first follow-up, GAD7-FU2 = GAD7 scores at 2nd follow-up.

Table 4: one way repeated measure ANOVA baseline and 1st follow-up assessments.

Intervention		Wilks Lambda (P)	Effect Size (Partial eta sq.)	Non-Intervention	Wilks Lambda (P)	Effect Size (Partial eta sq.)
Variable	M* (± SD)			M* (± SD)		
PATIENTS				PATIENTS		
PHQ9 – Base	4.29 (4.28)	0.001	.069	4.31 (4.27)	0.001	.057
PHQ9 – FU1	3.13 (3.44)			3.18 (3.70)		
GAD7 - Base	3.81 (3.68)	0.001	.031	3.81 (3.59)	0.001	.034
GAD7 – FU1	3.09 (3.00)			3.10 (3.01)		
CARE-GIVERS				CARE-GIVERS		
PHQ9 – Base	4.59 (4.27)	0.156	.012	3.63 (4.03)	0.238	.008
PHQ9 – FU1	4.04 (4.31)			3.26 (3.59)		
GAD7 - Base	3.79 (4.10)	0.842	.001	3.02 (3.43)	0.036	.026
GAD7 – FU1	3.85 (3.72)			3.67 (3.71)		

M = mean, SD = standard Deviation, PHQ9- Base = PHQ9 score at baseline, PHQ9-FU1 = PHQ9 scores at first follow-up, PHQ9-FU2 = PHQ9 scores at 2nd follow-up, GAD7- Base = GAD7 score at baseline, GAD7-FU1 = GAD7 scores at first follow-up, GAD7-FU2 = GAD7 scores at 2nd follow-up.

Changes in depression and anxiety in Care-givers

MANOVA analysis at baseline shows that there was no statistically significant difference between intervention and non-intervention on combined effect of depression and anxiety (p = .14). At 1st follow up there was a statistically significant difference between intervention and non-intervention on combined effect of depression and anxiety (p = .01). An inspection of the

mean scores indicated that non-intervention group reported slightly lower depression and anxiety scores. At 2nd follow-up the difference become insignificant (p = .09) (see table 3b).

Analysis of repeated measure ANOVA for care-givers shows that there was no significant effect for time in intervention group for depression (p = .15) and anxiety (p = .84). In non-intervention group there was a significant effect for time on anxiety scores (p = .03), however, effect for time on depression scores was insignificant (p = .23) (refer table 4). Repeated measure ANOVA analysis showed that there was no significant main effect for time on depression scores (p = .06), and anxiety (p = .11). The main effect comparing the intervention between the patients of intervention and non-intervention group was significant for depression scores (p = .01), whereas, it was insignificant for anxiety scores (p = .16). Exploring the mean scores indicated that intervention group reported slightly higher level of depression than non-intervention group at baseline assessment and 1st follow-up. The difference remains constant across two-time period, suggesting, that there was a significant difference in the mean scores of depression between the groups, but main effect for time was insignificant. The overall result suggest that intervention was not effective in reducing depression and anxiety in intervention group than non-intervention group.

Gender and the effectiveness of intervention among patients

MANOVA analysis for intervention group showed that there was a statistically significant difference between males and females on the combined effect of depression and anxiety at baseline assessment (p = .001), and at 1st follow-up (p = .001). However, the difference become insignificant at 2nd follow-up (p = .07). The mean scores for depression and anxiety was high among female patients at baseline, and on subsequent two follow-ups (see table 5a). The similar results were reported for non-intervention group at baseline assessment and at two follow ups.

The analysis of repeated measure ANOVA for baseline assessment and 1st follow-up, among intervention group shows that there was substantial main effect for time (p = .001), with both group (males and females) showing reduction in depression scores and anxiety scores across two-time period. The main effect comparing the two group at time 1 was also significant (p = .001), reporting higher mean scores of depression and anxiety among female patients of intervention group than male patients. The same trend was observed between male and female patients of non-intervention groups (see table 5a). The overall results suggest that intervention was not effective in reducing the depression and anxiety scores in intervention group than non-intervention group. There was similar reduction in depression and anxiety scores across two-time period (baseline and follow-up) among male and female patients in intervention and non-intervention group. Observation of mean scores however shows that females had significantly higher mean scores across both time points. (between subject effect, p = .001) for depression and anxiety than males in intervention and non-intervention patients (refer to table 6a).

Gender and the effectiveness of intervention among care-givers

MANOVA analysis for care-giver, intervention group, showed that there was a statistically significant difference between males and females on the combined effect of depression and anxiety at baseline assessment (p = .001), and at 1st follow-up (p = .001). However, the difference become insignificant at 2nd follow-up (p = .25). The mean scores for depression and anxiety was high among female care-givers at baseline, and on subsequent two follow-ups (refer table 3d). The similar results as in intervention group were reported for non-intervention group at baseline assessment and at two follow ups (refer 5b).

The analysis of repeated measure ANOVA among male and female care-givers of intervention group at baseline assessment and 1st follow-up shows that there was no significant main effect for time (p = .13 and p = .92 respectively). There was slight reduction in the mean

scores among male and females across two-time period but it did not reach statistical significance. Our results show that females were more depressed and anxious than males in intervention group. Similar results as in intervention group for depression and anxiety among male and female care-givers were reported for non- intervention group (see table 2c). At 1st follow-up there was a significant main effect for time (p = .04), with both group showing slight increase in the mean score of anxiety (see table 6b).

Age and the effectiveness of intervention among patients

MANOVA analysis for patients in intervention group showed that there was no statistically significant difference between young and old patients on the combined effect of depression and anxiety at baseline assessment (p = .13), at 1st follow-up (p = .21), and at 2nd follow-up (p = .79) (see table 3c). The similar results as in intervention group were reported for non-intervention group at baseline assessment and at two follow ups (see table 5a).

We analyzed if Age, age ≤ 40 years (referred here as young) and age > 40 years (referred here as old), moderate the effectiveness of intervention among patients. Our results show that there was a substantial main effect for time (p = .001 for depression, and p = .007 for anxiety) with both group (young and old aged) showing a reduction in depression and anxiety scores across the two-time period (see table 6a). The main effect comparing the two age groups was not significant, for depression and anxiety (p = .80, and p = .41) (see table 6a). Similar results as in intervention group for young and old patients were reported in non-intervention group (see table 6a). Our results show that the results were similar between intervention and non-intervention group for young and old patients, which suggests that our intervention was not effective in reducing depression and anxiety in intervention group compared with non-intervention group.

Age and the effectiveness of intervention among Care-givers

MANOVA analysis for patients in intervention group showed that there was no statistically significant difference between young and old patients on the combined effect of depression and anxiety at baseline assessment ($p = .54$), at 1st follow-up ($p = .70$), and at 2nd follow-up ($p = .50$) (see table 5b). The similar trend as in intervention group were reported for non-intervention group at baseline assessment and at two follow ups (see table 5b).

Our repeated measure ANOVA analysis shows that there was a no substantial main effect for time ($p = .15$ for depression, and $p = .007$ for anxiety) with both groups (young and old aged) showing a slight reduction in depression and anxiety scores across the two-time period (see table 6b). The main effect comparing the two age groups was not significant, for depression and anxiety, $p = .84$, and $p = .16$ respectively (see table 6b). Similar results as in intervention group for young and old patients were reported in non-intervention group (see table 6b). Our results show that the results were similar between intervention and non-intervention group for young and old patients, across two-time period (baseline assessment and 1st follow-up).

Table5a: Patients: Multivariate Analysis of Variance (MANOVA): the mean difference between male female on combination of depression and anxiety in intervention and non-intervention groups of patients and mean difference between young and old aged patient on combination of depression and anxiety

Intervention Group			Wilks Lambda (P)	Between Subject Effect (p)	Effect Size (Partial eta sq.)	**Non-Intervention Group**		Wilks Lambda (P)	Between Subject Effect (P)	Effect Size (Partial eta sq.)
Variable	**MALE** n: B=892, FU1=527, FU2=54	**FEMALE** n: B=460, FU1=288, FU2=20				**MALE** n: B=892, FU1=521, FU2=42	**FEMALE** n: B=467, FU1=697, FU2=52			
	M* (± SD)	M* (± SD)				M* (± SD)	M* (± SD)			
PHQ9 - Base	3.13 (3.55)	6.57 (5.11)	.001	.001	0.134	3.10 (3.56)	6.31 (4.58)	.001	.001	.132
GAD7 - Base	3.05 (3.11)	5.15 (4.10)		.001	0.075	3.02 (2.92)	5.00 (4.02)		.001	.074
PHQ9 – FU1	2.42 (3.04)	4.42 (3.76)	.001	.001	0.077	2.44 (3.22)	4.53 (4.13)	.001	.001	.073
GAD7 – FU1	2.53 (2.46)	4.13 (3.58)		.001	0.065	2.51 (2.55)	4.17 (3.48)		.001	.069
PHQ9 – FU1	2.78 (3.37)	4.25 (4.25)	.071	.125	0.032	2.98 (3.30)	5.21 (4.95)	.098	.042	.068
GAD7 – FU1	2.87 (3.07)	4.95 (4.11)		.022	0.071	3.33 (3.32)	4.42 (4.45)		.293	.019
AGE	Age (≤40 Yrs.) n: B=198, FU1=110, FU2=13	Age (> 40 Yrs.) n: B=1154, FU1=705, FU2=61				Age (≤40 Yrs.) n: B=176, FU1=117, FU2=09	Age (> 40 Yrs.) n: B=1129, FU1=697, FU2=52			
PHQ9 - Base	4.71 (5.08)	4.23 (4.33)	.129	.164	0.001	4.78 (4.63)	4.17 (4.18)	.121	.075	.002
GAD7 - Base	4.25 (3.96)	3.68 (3.55)		.043	0.003	4.20 (3.98)	3.66 (3.39)		.052	.003
PHQ9 – FU1	3.17 (3.62)	3.12 (3.41)	.210	.883	0.001	3.15 (3.96)	3.19 (3.66)	.941	.908	.001
GAD7 – FU1	3.47 (3.51)	3.03 (2.92)		.155	0.002	3.02 (2.80)	3.12 (3.05)		.744	.001
PHQ9 – FU1	2.69 (4.23)	3.28 (3.56)	.794	.604	0.004	3.67 (4.80)	3.67 (3.88)	1.00	.996	.001
GAD7 – FU1	2.85 (3.31)	3.56 (3.53)		.508	0.006	3.67 (2.45)	3.67 (3.90)		.996	.001

M = mean, PHQ9- Base = PHQ9 score at baseline, PHQ9-FU1 = PHQ9 scores at first follow-up, PHQ9-FU2 = PHQ9 scores at 2nd follow-up, GAD7- Base = GAD7 score at baseline, GAD7-FU1 = GAD7 scores at first follow-up, GAD7-FU2 = GAD7 scores at 2nd follow-up.

B = Baseline, FU1 = 1st Follow-up, FU2 = 2nd Follow-up

Table 5b: **Care-givers:** Multivariate Analysis of Variance (MANOVA): the mean difference between male and female care-givers on combination of depression and anxiety in intervention and non-intervention groups of care-givers and mean difference between young and old aged care-givers on combination of depression and anxiety.

Intervention Group			Wilks Lambda (P)	Between Subject Effect (P)	Effect Size (Partial eta sq.) (P)	**Non-Intervention Group**		Wilks Lambda (P)	Between Subject Effect (P)	Effect Size (Partial eta sq.)
Variable	**MALE** n: B=95, FU1=46, FU2=08	**FEMALE** n: B=184, FU1=116, FU2=24				**MALE** n: B=114, FU1=73, FU2=17	**FEMALE** n: B=166, FU1=99, FU2=18			
	M* (± SD)	M* (± SD)				M* (± SD)	M* (± SD)			
PHQ9 - Base	2.58 (2.99)	4.76 (4.60)	.001	.001	.060	2.33 (3.59)	4.07 (4.04)	.001	.001	.047
GAD7 - Base	2.73 (3.02)	3.88 (4.36)		.022	.020	2.26 (2.87)	3.42 (3.92)		.007	.026
PHQ9 – FU1	2.04 (2.86)	4.88 (4.54)	.001	.001	.091	2.56 (3.28)	3.77 (3.75)	.001	.029	.028
GAD7 – FU1	2.96 (2.63)	4.23 (4.05)		.044	.025	3.11 (3.07)	4.09 (4.08)		.087	.017
PHQ9 – FU1	4.38 (4.98)	4.29 (4.00)	.250	.962	.001	2.71 (4.21)	2.50 (2.40)	.924	.859	.001
GAD7 – FU1	3.13 (3.83)	4.92 (4.05)		.282	.039	2.18 (2.67)	2.33 (3.48)		.883	.001
AGE	Age (≤40 Yrs.) n: B=165, FU1=95, FU2=14	Age (> 40 Yrs.) n: B=114, FU1=70, FU2=18				Age (≤40 Yrs.) n: B=164, FU1=95, FU2=21	Age (> 40 Yrs.) n: B=116, FU1=77, FU2=14			
PHQ9 - Base	4.06 (4.47)	3.95 (3.92)	.540	.827	.001	3.20 (3.93)	3.59 (3.98)	.112	.423	.002
GAD7 - Base	3.68 (4.30)	3.21 (3.48)		.336	.003	3.13 (3.79)	2.69 (3.22)		.305	.004
PHQ9 – FU1	4.11 (4.66)	3.94 (3.81)	.700	.812	.001	3.09 (3.52)	3.45 (3.70)	.060	.520	.002
GAD7 – FU1	4.04 (3.94)	3.60 (3.41)		.453	.003	4.05 (4.05)	3.21 (3.21)		.138	.013
PHQ9 – FU1	4.00 (5.20)	4.56 (3.30)	.507	.716	.004	2.05 (2.33)	3.43 (4.45)	.099	.238	.042
GAD7 – FU1	4.86 (4.57)	4.17 (3.63)		.637	.008	2.48 (3.23)	1.93 (2.89)		.613	.008

M = mean, PHQ9- Base = PHQ9 score at baseline, PHQ9-FU1 = PHQ9 scores at first follow-up, PHQ9-FU2 = PHQ9 scores at 2nd follow-up, GAD7- Base = GAD7 score at baseline, GAD7-FU1 = GAD7 scores at first follow-up, GAD7-FU2 = GAD7 scores at 2nd follow-up.

Table 6a: Patients: Mixed between-within subject ANOVA: Assess the effect of intervention between male and female patients, and between young and old patients.

Group	M* (±SD)	M* (±SD)	Wilks Lambda Time - (P)	Between Subject Effect (P)	Effect Size (Partial eta sq.)
INTERVENTION	***Male (n = 527)***	***Female (n = 288)***			
PHQ9 - Base PHQ9 – FU1	3.23 (3.60) 2.42 (3.76)	6.23 (4.72) 4.42 (3.76)	.001	.001	.140
Gad7 – Base GAD7 – FU1	3.06 (3.16) 2.53 (2.46)	5.18 (4.15) 4.13 (3.58)	.001	.001	.110
Non-Intervention	(n = 521)	(n = 287)			
PHQ9 - Base PHQ9 – FU1	3.31 (3.86) 2.44 (3.22)	6.14 (4.39) 4.53 (4.12)	.001	.001	.130
Gad7 – Base GAD7 – FU1	3.15 (3.17) 2.51 (2.54)	5.01 (3.98) 4.17 (3.47)	.001	.001	.100
INTERVENTION	***Age ≤ 40 yrs.) (n = 110)***	***Age > 40 yrs.) (n = 705)***			
PHQ9 - Base PHQ9 – FU1	4.10 (4.19) 3.17 (3.62)	4.32 (4.29) 3.12 (3.41)	.001	.804	.001
Gad7 – Base GAD7 – FU1	3.82 (3.41) 3.47 (3.51)	3.80 (3.72) 3.03 (2.92)	.007	.410	.001
Non-Intervention	(n = 117)	(n = 691)			.001
PHQ9 - Base PHQ9 – FU1	4.91 (4.76) 3.15 (3.65)	4.21 (4.18) 3.19 (3.66)	.001	.310	
Gad7 – Base GAD7 – FU1	4.21 (4.10) 3.02 (2.79)	3.74 (3.50) 3.12 (3.05)	.001	.500	.001

M = mean, PHQ9- Base = PHQ9 score at baseline, PHQ9-FU1 = PHQ9 scores at first follow-up, GAD7- Base = GAD7 score at baseline, GAD7-FU1 = GAD7 scores at first follow-up.

Table 6b: Care-Givers: Mixed between-within subject ANOVA: Assess the effect of intervention between male and female care-givers, and between young and old care-givers.

Group	M* (±SD)	M* (±SD)	Wilks Lambda Time - (p)	Between Subject Effect (p)	Effect Size (Partial eta sq.)
INTERVENTION	***Male (n = 49)***	***Female (n = 116)***			
PHQ9 - Base PHQ9 – FU1	2.90 (2.98) 2.04 (2.86)	5.31 (4.53) 4.88 (4.54)	.130	.001	.120
Gad7 – Base GAD7 – FU1	3.00 (3.28) 2.96 (2.63)	4.12 (4.37) 4.23 (4.05)	.920	.030	.028
Non-Intervention	(n = 73)	(n = 99)			
PHQ9 - Base PHQ9 – FU1	2.84 (4.10) 2.56 (3.28)	4.21 (3.89) 3.77 (3.80)	.260	.009	.040
Gad7 – Base GAD7 – FU1	2.58 (3.22) 3.11 (3.07)	3.34 (3.56) 4.09 (4.08)	.040	.540	.220
INTERVENTION	***Age (≤ 40 yrs.) (n = 95)***	***Age (> 40 yrs.) (n = 70)***			
PHQ9 - Base PHQ9 – FU1	4.62 (4.57) 4.11 (4.66)	4.56 (3.86) 3.94 (3.81)	.150	.840	.001
Gad7 – Base GAD7 – FU1	4.22 (4.64) 4.04 (3.95)	3.20 (3.18) 3.60 (3.42)	.740	.160	.012
Non-Intervention	(n = 90)	(n = 68)			
PHQ9 - Base PHQ9 – FU1	3.24 (3.83) 3.09 (3.52)	4.10 (4.24) 3.45 (3.70)	.210	.220	.009
Gad7 – Base GAD7 – FU1	3.02 (3.61) 4.05 (4.05)	3.01 (3.23) 3.21 (3.21)	.051	.350	.005

M = mean, PHQ9- Base = PHQ9 score at baseline, PHQ9-FU1 = PHQ9 scores at first follow-up, GAD7- Base = GAD7 score at baseline, GAD7-FU1 = GAD7 scores at first follow-up.

DISCUSSION:

This randomized clinical trial was designed to investigate the usefulness of mobile phone SMS capability to educate CAD patients and their respective care givers for psychological wellbeing. The results of this clinical trial shows that there was no statistically significant difference in the mean scores of PHQ9 and GAD7 between intervention and non-intervention groups of patients and care givers. The difference was not statistically significant at baseline and at two follow-ups, indicating that our SMS text messages for psychological wellbeing failed to achieve their desired objective. Our study showed that females were more depressed and anxious than males, and that difference in gender remained constant across baseline assessment and subsequent follow-ups.

The results of our study found that majority of the patients in intervention and non-intervention groups were not depressed (63%). However, approximately 25% of the patients experienced mild symptoms of depression with approximately 12% experiencing moderate to severe depression at baseline. Similarly, approximately 21% of the CAD patients in this study reported mild levels of generalized anxiety, while 8% experienced moderate to severe levels of anxiety. The trend was almost similar at subsequent follow-ups. Female participants in this study experienced higher levels of depressive and anxious symptoms than male participants.

The prevalence rates of depression and anxiety from our study are consistent with similar studies conducted in Pakistan and other region of the world [165-167]. A study conducted in Pakistan in CAD patients, reported that 27% of their study subjects were positive for depression on PHQ-9 scale [139]. A study conducted by Liang J. J. et al. in USA reported depression in 33% of cardiac patients, whereas, 37% suffered from anxiety [137]. Previous studies also confirmed that depression was more common and severe in females than males [140, 168-170]. Study conducted in USA reported that approximately 20% of their CAD patients were diagnosed with depression [171, 172]. Anxiety comorbid with depression increases mortality among CAD patients. A study conducted in USA reported that CAD patients' comorbid with

anxiety symptoms showed two-fold increase in mortality [144]. A cross sectional study conducted in Saudi Arabia among primary care patients showed that 50% suffered from depression (31% had mild depression)[138].

Among care-givers of our study, there was no significant difference between intervention and non-intervention groups in the prevalence of depression and anxiety at baseline. Among intervention 37% had mild to severe depression, whereas in non-intervention group 30% had mild to severe depression. Mild to severe GAD was prevalent in 29% of intervention group, and 22% had it in non-intervention group. Study conducted by Karin Oechsle et al. utilized GAD7 and PHQ9 to assess anxiety and depression in caregivers of terminally ill cancer patients[154]. The result of that study showed that 55% of the male and 36% of female caregivers were positive for moderate or severe anxiety, and 36% of the male caregivers as compared to 14% of the female caregivers suffered depression[154]. Caregivers' anxiety and depression were significantly correlated in their study. It has been reported that around 4% of the general population of USA suffered major depression in 2008[154]. Another study reported 76% of anxiety and 77% of depression among family caregivers of patients in palliative care[173]. One study conducted in three provincial capital cities of Pakistan reported regional variation in the prevalence of depression; Lahore (53.4%), Quetta (49.3%), and Karachi (35.7%) [164]. That study explained the difference in the prevalence of depression in three different geographical areas as e attributed to local cultural influence, geographical locations, and social adversities.

The results from our study showed that our SMS based intervention did not have any effect in the reduction of depression and anxiety among our intervention group as compared to our non-intervention group in both CAD patients and caregivers. Although numerically there was a slight reduction in the mean scores of PHQ9 and GAD7 from baseline to follow-ups in both patient and caregivers, the trend was similar in intervention and non-intervention group,

suggesting our intervention was not effective in significantly improving the psychological wellbeing of our intervention group. The potential explanation for our intervention not to achieve its' desired goal could be that text based messages are not convincing enough to promote psychological wellbeing. Secondly, the short duration of the intervention may have contributed in its failure. The study conducted by Agyapong et al. to observe the effective of their supportive mobile phone text messages to patients with depression and comorbid alcohol use disorder, found that their intervention was not effective in reducing depression after 3 months of intervention [174]. The explanation provided by the authors was that the effects of the intervention were not sustained beyond the period that the patients actually received the intervention [174]. The authors recommended long term intervention for the effect of the intervention to be sustainable [174]. Our study supported the findings of other studies, that female suffer more from anxiety and depression than male [45, 140].

To the best of our knowledge this is the first study designed to utilize a mobile phone SMS based intervention for psychological wellbeing in CAD patients, and in particular the first to do so in a Pakistani population. As such it is difficult to directly compare our results with other studies. Few studies have shown successful results using telephone-delivered cognitive behavioral therapy to depressed and anxious CAD patients [75, 175-181]. Though, telephone-delivered cognitive behavioral therapy is a different intervention compared to mobile phone text based psychological wellbeing, but both interventions could be combined for a long term benefit. As such there appears to be emerging evidence that SMS interventions alone may not be powerful enough to result in changes in depressive or anxious symptoms in CAD patients and caregivers, as well as the wider population.

Strength and Limitations:

The major strength of our study is its sample size. To the best of our knowledge, this study is one of the largest mobile phone text messages based intervention in CAD patients conducted

in SA. The other major strength is the inclusion of the respective patient's primary care givers, not only to target primary prevention but to have bi-directional reinforcement of health messages.

There are several limitations to account for in interpreting our results. The major limitation was rather high drop-out rate at follow-up. The low follow-up rate is in relation to the patients recruited in the study (2656) which is more than our calculated sample size for patients (1540). Despite our best effort to persuade our study participants to visit our study site for follow-up, only two thirds of the participants were able to complete first follow-up of 66%., whereas for calculated sample size it was The main reason given by the participants was the safety and security situation in Karachi, which restricted their ability to travel. In addition, due to financial constraint, we were unable to continue to offer free laboratory investigations to many of the participants, nor did we have finances to compensate for the travel expenses at the follow-ups. The other limitation was that we only recruited the survived (non-fatal) patients of CAD, so our result could only be attributed to survived patients, not to be generalized on the whole population of CAD patients who reached to the hospital. Finally, our study's follow-up was limited to an average of six months, which turned out to be not long enough to collect a sufficiently large sample of deceased participants, due to a low mortality rate in our study participants.

Recommendation:

There is convincing evidence that depression and anxiety is related with the incidence of CAD and its outcomes, suggesting that treatment could greatly benefit in the prevention of CAD. While our intervention was unable to show a significant reduction in mortality by use of SMS, given the large body of evidence showing depression and anxiety as risk factors for mortality and future cardiac events, there is good rationale to continue to explore cost-effective and sustainable interventions for depression and anxiety in CAD patients. One of the probable

solutions to help make text messaging as an effective intervention for the psychological wellbeing among CAD patients and their caregiver, could be to combine it with the proven beneficial preventive strategies. The combination could be initial short term face to face psychotherapy, with mid-term telephone-delivered psychological health coaching, and then sustaining it with long term positive reinforcing psychological wellbeing mobile phone text messaging the other combination could be a short term face to face psychotherapy and then long term support with internet based health education, social media support (like, facebook, WhatsApp, Skype etc.) and supportive text messages. These combination of multiple interventions may prove to be effective, sustainable and cost effective. Further research on recommended strategies may benefit in promoting the psychological wellbeing of the CAD patients and their caregivers.

Conclusion

The effectiveness of text based intervention to promote healthy lifestyle to reduce CAD has been reported recently, but, to best of our knowledge, that intervention has not been implemented to promote psychological wellbeing in CAD patients. It is somewhat surprising that SMS based intervention was not effective in our study subjects. The potential explanation for the non-effectiveness of our intervention may be explained as first, the majority (more than 63%) of study subjects) scored as not being suffering from depression or anxiety, and those who had symptoms of depression or anxiety, majority of them were mildly depressed (more than 90%). This left us with little room for improvement, and text messages alone may not be convincing enough to have positive impact on their psychological wellbeing. Second, even though we can increase the length of message by increasing the character but it would increase the cost of the message as each message is cost by count of characters in a message. Third, individuals to be diagnosed as suffering from anxiety and depression even in the presence of standardized screening tools/instruments could reflect a recall bias, as one of the limitation

[182]. Fourth, it has been acknowledged that by previous studies that participants may be reluctant to acknowledge a formal diagnosis of anxiety or depression because of the stigma associated with mental illness [183-186]. Studies conducted in Pakistan reported that participants hide their true feelings due to social stigma, as people surrounding them have negative feeling about it [187, 188]. The above mentioned biases could also have influenced the outcome of our study too. Fifth, different geographical areas (even in one country) and culture can influence the prevalence of depression and anxiety. A study conducted in three provincial capital cities of Pakistan reported prevalence of depression in Lahore at 53.4%, in Quetta (43.9%), and in Karachi (35.7) [164]. It was surprising to note that Karachi with relatively worst safety and security situation, violence, street crimes, terrorism and lawlessness showed relatively lowest prevalence of depression, whereas in Lahore, where safety and security situation is relatively better, and had wider exposure to psychiatric services, people are more expressive and had the highest proportion of people with depression as compared to other two cities. The explanation provided by the study was, that geographical area, language, and cultural background can influence the prevalence rate of depression and anxiety in that population [164].

Even though, our SMS based intervention was not effective in promoting psychological wellbeing in our intervention group of CAD patients and their caregivers, but it may provide an opportunity to rethink about implementing said intervention in a different way, and may be considering all the issues discussed earlier, for it to be effective for psychological wellbeing of the CAD patients and their caregivers.

Competing interest:

No competing interest was declared by the authors.

Trial Registration:

The clinical trial is registered at Australia New Zealand Clinical Trial Registry (Reg. No: ACTRN12611000388910.)

Funding/Support:

The study was funded by a research grant from the Cardiac Health Institute, Sydney. Pathology studies were partially subsidized by Essa Diagnostic Laboratory, Pakistan

AUTHORS' CONTRIBUTION

Study Concept and Design:	Ismail
Protocol development and review:	Ismail, Kiat, Strodl, Ansari, Jun Ma
Macquarie University Ethics application:	Ismail, Kiat
Study sites approval & IRB:	Ismail, Kiat
Data collection and management:	Ismail
Drafting of the manuscript:	Ismail
Critical revision of the manuscript:	All authors
Statistical analysis:	Ismail, Strodl, Jun Ma
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ACKNOWLEDGMENT

We are thankful to all study participants to consent in the study and shared their experiences throughout the trial, as without their cooperation we would not have be able to get insight for our objectives. We acknowledge the contribution of our research assistants, Ms. Mehreen Aziz, Ms. Javeria Saeed, Ms. Yusra Iqbal, Ms. Safia, and Ms. in collecting the data for the study.

We are grateful for Essa Diagnostic Laboratory for providing the laboratory investigations on discounted rates. We appreciate the cooperation of all our participating study sites.

CHAPTER 4:

Mobile Phone-Assisted Lifestyle Modifications to Reduce Mortality Due to Coronary Heart Disease – Randomized Controlled Clinical Trial

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Title:

Mobile Phone-Assisted Lifestyle Modifications to Reduce Mortality Due to Coronary Heart Disease – Randomized Controlled Clinical Trial

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Key Words:

Cardiovascular disease	(CVD)
Coronary Artery Disease	(CAD)
Diabetes Mellitus	(DM)
Disability-Adjusted Life-Years	(DALYs)
Electro Cardio-Gram	(ECG)
Generalized Anxiety Disorder	(GAD)
Hypertension	(HTN)
Karachi Institute of Heart Diseases	(KIHD)
Mobile Health	(mHealth)
Multimedia Message service	(MMS)
Myocardial Infarction	(MI)
National Institute of Cardiovascular Diseases	(NICVD)
Non Communicable Diseases	(NCD)
Patients Health Questionnaire	(PHQ)
Randomized Clinical Trial	(RCT)
Research Assistant	(RA)
Short Message Service	(SMS)
South Asian	(SA)
Tabba Heart Institute	(THI)
Usual care and Intervention group	(IG)
No-intervention group	(NIG)
World Health Organization	(WHO)

Mobile Phone-Assisted Lifestyle Modifications to Reduce Mortality Due to Coronary Heart Disease – Randomized Controlled Clinical Trial

ABSTRACT:

Background:

Cardiovascular disease is the leading cause of deaths globally, especially in South Asian countries. Coronary Artery Disease (CAD) has a high prevalence in Pakistan and is a major cause of premature mortality in this country. Unhealthy diet, cigarette smoking, pollution, sedentary lifestyle, and psychological factors such as depression and anxiety are among the major modifiable risk factors. With the rapid advances and dissemination of mobile communication, SMS messaging holds promise as an affordable, effective and far-reaching means to affect behavioral changes in personalized health education, and health care management.

Objective:

To explore the effectiveness of a mobile phone text messaging intervention program to reduce mortality in coronary artery disease patients.

Methodology:

A randomized, controlled, clinical trial was conducted in 3 cardiac specific tertiary care hospitals in Karachi, Pakistan. Participants were patients who had their first cardiac events and their respective nominated care-givers. Patients and their care-givers were randomized into two groups, intervention (IG) or usual care group with no-intervention (NIG). For the participants in the IG daily health text messages were sent to their mobile phones, 5 days per week. Patients in both groups were followed up at 6 monthly intervals.

Results:

In total, there were 86 (3.2%) deaths over the course of the study, 41 deaths in intervention and 45 deaths in non-intervention groups. Care-givers were excluded from the analysis as there were no deaths among them. Kaplan-Meier survival analysis showed that mean survival time (534 days) in intervention group and mean survival time (514 days) in non-intervention was not significantly different. Cox-regression analysis showed old age, unemployment, history of diabetes, and hypertension and non-physical activity were independently associated with mortality in first ever CAD patients.

Conclusions:

Our intervention of mobile phone text messaging to promote healthy lifestyle was not effective in reducing the mortality among CAD patients in Pakistan who presented for the first time with a coronary event. Future interventions for CAD patients with their first cardiac event, living in Pakistan, should specifically target the modifiable risk factors of unemployment, management of diabetes and hypertension and non-physical activity in order to reduce the risk of premature mortality in this population.

Key words: coronary artery diseases, caregivers, text messages, intervention, mortality, clinical trial, Disability Adjusted Life Year Lost

TITLE:

Mobile phone-assisted lifestyle modifications to reduce mortality due to coronary heart disease – randomized controlled clinical trial.

SHORT TITLE: TEXT2PREVENT

INTRODUCTION:

Thirty-one percent (17.5 million) of all global deaths in 2012 were due to CVD and among CVD deaths, 7.4 million deaths were due to coronary artery disease (CAD) [1, 2]. While CAD is the single largest cause of death in developed countries, it is also one of the leading causes of death in developing countries [1-3]. Three-quarters of global deaths due to CAD (nearly 80%) occurred in low and middle-income countries, the majority of which were considered premature deaths (under the age of 70 years) [1-5]. South Asians (India, Pakistan, Bangladesh, and Sri Lanka) comprises 25% of the world's population and suffers from nearly 60% of the global CVD burden [6-8]. Global burden of disease (GBD) 2010 reported that South Asian countries had the high CAD burden, and more than 29% of men and 24% of women who suffered CAD were < 50 years-old [9]. CAD in South Asians occurs at a younger age, is more aggressive, and has a higher overall mortality [10-12] . The South Asia region had the highest number of life-year lost to premature CAD [13]. Premature CAD deaths indicate that it is more likely to occur in productive, working-age adults, which represents the greatest loss for families and national economics [14]. The age of onset of first CAD among SA population, on an average, is 10 years earlier compared with other populations, and this is largely attributable to higher prevalence of CAD risk factors at younger ages [15]. Studies among SA migrant have found that the mortality rate attributable to CAD among SA younger than 30 years is 3 fold higher than for Caucasians in the United Kingdom and 10-fold higher than the Chinese in Singapore [16, 17]. It has been reported that the likelihood of developing CAD in South Asians is about 2 time higher than in European and 5 time higher than Chinese [6, 18, 19]. In 2005,

the estimated mortality associated with CVD was 29% in India [20]. Pakistan with more than 185 million people is the sixth most populous country in the world [22]. Data from Pakistan in the GBD 2010 study showed that CVD was responsible for 18% of crude deaths and 26% of age standardized deaths, making them the leading cause of deaths in individuals within a productive age group of 30 – 69 years [21]. It has been suggested that one in four middle-aged adults in Pakistan has prevalent CAD [25]. The projected crude yearly mortality per 100000 populations in Pakistan from 2010 to 2025 for CVD was reported to increase from 125.5 in 2010 to 144.4 in 2025 [22]. The cumulative deaths from CVD, cancers and chronic respiratory diseases in people aged 30 – 69 from 2010 to 2025, in Pakistan is predicted to be 3.87 million [22]

A large epidemiological case-control study, INTERHEART, suggest that 90% of the attributable risk for CAD can be explained by 9 behavioral and physiological risk factors. The 9 risk factors are 1) low consumption of fruits and vegetables 2) tobacco smoking; 3) alcohol consumption; 4) psychosocial factors; 5) sedentary lifestyle; 6) hypertension; 7) dyslipidemia; 8) abdominal obesity; and 9) diabetes [23]. Previous studies have reported that the South Asian population who suffered from CAD had an increase prevalence of tobacco smoking, low consumption of fruits and vegetables, decreased physical activity, high level of stress and other psychosocial risk factors, diabetes, hypertension [15, 20, 24-27]. The GBD 2013 study stated that major risk factors associated with CAD are modifiable indicating a huge potential for prevention [29]. At least 80% of premature deaths from heart disease can be avoided by engaging in regular physical activity, avoiding tobacco use and second-hand tobacco smoke, choosing a diet rich in fruit and vegetables, avoiding foods that are high in fat, sugar and salt, and maintaining a healthy body weight [30]. A recent study found that 4 out of 5 myocardial infarctions (MIs) in men could be prevented by following a healthy diet, being physical active (walking/bicycling ≥ 40 min/day and exercising ≥ 1 hr./week), moderate alcohol use (10 - 30

g/day), having no abdominal adiposity (waist circumference < 95 cm), and refraining from smoking[31]. In addition, over the last couple of decades, a sleuth of studies also identified depression, anxiety and other psychosocial factors, including nonphysical stress as potent risk factors for CVD, associated with an increased risk of mortality [32-36]. These established risk factors are therefore important to target in any intervention aimed at reducing mortality rates in CAD patients.

National Health Survey of Pakistan (NHSP) 1990 – 94 reported that the prevalence of hypertension in adults (≥ 15 years) was 18%, one in four were overweight (BMI > 23kg/m^2), and 90% of the population did not consume the targeted 5 servings of fruits and vegetables [41-43]. Pakistan Diabetes Survey (PDS) showed prevalence of diabetes in adults ≥ 25 years was 22% in urban areas [44]. Prevalence of anxiety and depression in adult population of Pakistan was reported to be 34% (range 29% – 66% for women and 10% – 33% for men) [45]. In Pakistan only 3% – 6% of hypertensive are under satisfactory control [46, 47]. A systematic analysis of 2013 study stated that in 2013 dietary risks accounting for 11.3 million deaths and 241.4 million disability-adjusted life-years (DALYs), high systolic blood pressure for 10.4 million deaths and 208.1 million DALYs, tobacco smoke for 6.1 million deaths and 143.5 million DALYs, and high BMI for 4.4 million deaths and 134.0 million DALYs [29]. Given these high prevalence rates of risk factors, there is an urgent need to develop an effective intervention to reduce these risk factors in the Pakistani population.

It has been projected that the number of attributable deaths in Pakistan from NCD in 2025 in all adults aged 30 – 69 years can be averted if key risk factors were reduced by their specified levels [22]. The authors estimated that the most substantial reduction in the number of deaths could be attained with the reduction of mean systolic blood pressure by 3 mmHg (20700 deaths), whereas 30% reduction in the prevalence of tobacco use could avert 19500 deaths, reduction in fasting blood glucose level by 0.25 mmol/L (11200 deaths) reduction in body mass

index by 0.15 kg/m^2 (8800 death) increase in physical activity to 50% of recommended level (6500 deaths), and increase in intake of fruits and vegetables by 50 g/day could avert 3000 deaths[22]. Cumulative reduction at specified level by all seven risk factors the specified total reduction in 62700 deaths in 2025, and 623900 from 2015 to 2025 [22]. Current health system in Pakistan is unable to manage the increasing burden of NCD, with total per person expenditure of less than a total US$18 per year, which is lower than neighboring India and Sri Lanka [22]. There is no separate budget allocated for prevention and rehabilitation program for NCD [22]. WHO and Non-communicable disease alliance recommended 25% reduction in overall mortality rate from CVD, cancers diabetes and chronic respiratory diseases in adults aged 30 – 70 years [48]. Given the current health system in Pakistan it is suggested that 20% reduction in NCD mortality by 2025 would be reasonable target [22]. It has been projected that if an effective intervention could be implemented for the combined reduction in the risk factors of tobacco use, systolic blood pressure , cholesterol, and diabetes, it could avert 730000 deaths from projected 3870000 due to CVD, in individuals aged 30 – 69 years, at different time points in Pakistan from 2010 to 2025 [22]. Several reports examined national capacities to implement CVD prevention and treatment program and concluded that in majority of the countries there was little prevention strategies to combat CVD epidemic or will to take action [49, 50].

Given the high prevalence of these modifiable risk factors for CAD mortality within the Pakistani population, there is an urgent need to develop cost-effective and sustainable interventions to help reduce these risk factors for CAD.

Changing modifiable risk factors, however, is not straightforward with many primary and secondary preventive strategies failing to achieve their desired goals [58, 59]. The WHO-PREMISE project showed that a significant number of patients fail to adopt healthy lifestyle habits after a major cardiovascular event, with 12.5% of the studied patients continuing to smoke, 38.4% not complying with dietary advice, and 52.5% not engaging in regular physical

activity [59]. The results of the WHO-PREMISE project underscore the need for novel strategies to improve compliance and persistence in risk factor modification measures. Numerous studies conducted in UK and USA have reported a general deficit in knowledge concerning CAD, its prevention and health promotion among SA immigrants [60, 61]. In Pakistan, where there is a high and increasing prevalence of CAD, and the majority of the population lacks substantive knowledge on risk reduction related lifestyle modification measures [62, 63]. It is not only that the general population's lack of knowledge on CAD risk reduction is high, but also that health professionals fail to educate their patients. For example, seventy-five percent of Pakistan's population consult private family physicians for their primary health care, but there are serious deficiencies in family physician's knowledge, management, and prevention of hypertension and CVD [54]. Knowledge on risk reduction related lifestyle modification is the key to reduce the burden related to CAD.

It is recommended that to be successful in reducing the mortality due to CAD in 21st century, as many high-income countries did during the last decade of 20th century, low and middle-income countries will now need to develop new innovative population wide preventive strategies [66]. With the rapid advancement in tele-media access, new technologies provide the potential for more cost effective and efficiently delivered health care interventions. One such promising technology is the mobile phone technology, referred as mHealth [65] which include text messaging, video messaging, video calling, and internet connectivity [66, 67].

Mobile phones support two-way synchronous conversation (voice calling) and durable textual communication (Short Message Service, SMS). Mobile phone text messaging has a great potential as a tool for improvement of preventative health care. It is easy to execute, low cost, and the service is available in all contemporary mobile phones. SMS widespread use, its ability to present succinct and instantaneous yet durable information makes text messaging suitable for a wide variety of health care management measures [66, 68]. Advantages of text

messaging includes ready access of information when and wherever convenient to the patients [66], and the reliability of delivery (even if the phone is turned off when the message is delivered the patient will still receive it upon turning the phone on) [69]. Text messaging is particularly suitable for behavioral interventions because it allows for in-the-moment, personally tailored health communication and reinforcement. Recent studies have found that periodic prompts, and reminders are effective methods to encourage and reinforce healthy behaviors [70, 71].

The number of mobile phone users in Pakistan reached 136.5 million mark at the end of March 2014, and this number continues to grow at a fast pace [77-79]. In 2011, the number of text messages exchanged in Pakistan jumped to 238 billion from 152 billion in 2010, illustrating the upwards trend in SMS usage [80]. Importantly, mobile phones also have huge penetration in rural areas of Pakistan. As a result, mHealth has the potential to deliver healthcare programs to the entire population of Pakistan.

It has been identified that there is a deficit in knowledge regarding CAD and its prevention in Pakistan, and in the context of the present health care system of Pakistan, with limited resources, competing priorities and lack of will to fund preventive programs to reduce the burden of CAD, it is now imperative to target preventive strategies that are affordable, feasible, and have the highest probabilities of success. The method of delivering health and lifestyle modification information on individual and community level should be affordable, accessible, wide reaching and sustainable for a longer period which can improve health outcome. We have therefore undertaken to design a mobile phone text message health education intervention to promote adoption of positive lifestyle to reduce major risk factors attributed to CAD, which in turn reduce the mortality rate in first ever CAD patients

METHODOLOGY:

Trial Design

The study was designed as a randomized, controlled, single blinded clinical trial.

Participants

The study subjects comprised of cardiac patients who had suffered their first non-fatal cardiac event related to CAD, and admitted in one of our participatory study hospitals. The participants were of both gender, and above 17 years of age.

Eligibility criteria for participants

Participants were recruited if they were in a sound state of mind (i.e. no self-reported symptoms of psychosis, delirium, and dementia, and could communicate in a coherent way), were willing to participate in the study, had stable cardiac status at discharge, owned a personal mobile phone with a personal SIM (subscriber identification module), were willing to retain the same SIM during the study period (or were willing to inform the investigators if their phone number changed), understood the basic operations of a mobile phone, could read text messages, and did not have any significant life-threatening co-morbidities (such as terminal cancer or end-stage renal disease). Participants were excluded if they did not own a mobile phone and were unwilling to acquire one, were pregnant females, or were below the age of 18 years old.

Study Sites

The study was conducted at the three tertiary care cardiac specific hospitals with basic and advanced facilities for cardiac care in Karachi: National Institute of Cardiovascular Diseases (NICVD), Karachi Institute of Heart Diseases (KIHD), and Tabba Heart Institute (THI). The entire population of Karachi falls into the catchment of these three cardiac hospitals.

Intervention

Mobile phones were used to deliver positive behavioral change/lifestyle modification health messages to the intervention group by SMS. The text messages (SMS) were based upon knowledge/motivational statements taken from primary and secondary prevention programs for CAD that are based on guidelines developed by WHO and the National Heart Foundation of Australia [32, 33, 96]. The pool of health messages was developed by the study investigators. The messages were pilot tested in 300 subjects and assessed for their level of comprehensibility and comfort. Messages that were not easily understood were re-worded to eliminate ambiguity. Some of the messages sent to the IG in lay language are as follows;

- Quit tobacco use, reduce the amount smoked, or do not start the habit;
- Smoking tobacco is injurious to your health, especially for heart.
- Be physically active (at least 30 minutes on most week days);
- If you are fit, climb the stairs instead of taking the escalator or elevator, get off the bus, a stop earlier and walk,
- Park the car further away from your destination, walk to the corner store, bank and post office. Stand while talking on the mobile phone
- Make healthy food choices;
- Increase vegetable intake; they are a healthy source of vitamins, minerals & fiber.
- Reduce your total intake of fats, use sugars and sweets sparingly
- Four golden rules to help avoid high blood pressure – weight control, positive lifestyle, healthy diet, medical check up

Messages were also sent to participants in the IG to remind them of their appointment schedule and to adhere to their prescribed medications. Messages were limited to 160 characters and were phrased in layman terminology. During the initial 6 months following enrollment, one message was delivered every weekday, targeting one risk factor per day in a

cyclical fashion. After 6 months, the frequency was increased to 2 or 3 messages per day, 5 days per week, each targeting a different risk factor. Around 60% of the messages were motivational, 30% were knowledge based and 10% were reminders for follow-ups. In contrast, the NIG received general greeting messages, including thanking them for being in the study, and reminders about their follow-up appointments. These messages were sent out fortnightly.

The communication was of a two-way nature. Participants were encouraged to send general enquiries about major risk factors by SMS. One of the investigators, Javed Ismail (JI) responded to their queries within 48 hours. Voice calls were also responded to where possible. Via SMS queries from the IG were replied in detail, whereas lifestyle modifications related queries from the NIG were not answered specifically. Instead, they were advised to consult their treating physician. Members from either group with queries relating to specific health conditions, including medications and symptoms were directed to their treating physicians. The study was not designed to evaluate the pharmacologic therapies administered to the patients by their treating physicians and did not interfere with their routine medical care. Information derived from this study was not made available to the treating health care professionals of the participants. Around 80% of the queries were via phone calls and 10% were by SMS.

Outcome Measure

The Primary outcome measures were mortality due to cardiac cause, composite cardiovascular mortality (stroke, myocardial infarction, or death from any cardiovascular cause) whichever occurs first. If the cause of death is unknown, that was recorded as 'presumed cardiovascular death – cause unknown', and readmission to a hospital due to CAD-related events.

Sample Size

The sample size was calculated based on the dichotomous primary outcome variables (mortality and readmission). Previous studies have shown that mortality due to cardiovascular

diseases in Pakistan was 8% to 29% [97, 98]. To capture the least prevailing associated risk factor, the sample size was calculated based on a mortality of 15% due to CAD.

With 80% power, 5% significance level, and 10% difference (from 15% to 5%) in the mortality rate between groups, the calculated sample size was 700 patients in each group. After assuming a 10% attrition rate, the final sample size was determined as 770 patients in each group (1540 total). Because there was one primary caregiver for every patient, the same sample size was assumed for caregivers. As a result, the total sample size deemed appropriate was 3080 with 1540 subjects each for patients and caregivers.

Randomization

Patients were randomly assigned to the intervention group (IG) or the non-intervention group (NIG). The IG received lifestyle modification education via text messages. The NIG received "neutral messages" consisting of greeting/salutation, and reminder of follow-up dates and time, once per week.

Sequence generation and allocation concealment mechanism

A randomization list of 100 subjects for each site was generated in STaTa software, with equal numbers of participants in the IG and NIG. The subjects were randomized by their study registration number. The list was kept with one of the study investigators, Javed Ismail (JI), who supervised the data collection but did not have direct personal contact with the subjects at the time of baseline recruitment. Research Assistants (RAs) subjects a consecutive study registration number, and sent their questionnaire with the allotted study registration number to the main study office at KIHD. JI assigned each patient a group (IG or NIG) as per the randomization list. The delivery of behavioral change SMS text messages, and replies to the queries of the study subjects were done by JI.

Blinding

RAs were blinded from a participant's assigned group until close to the trial, whereas, JI was blinded to the baseline health status of the subjects. At follow-ups, RAs were instructed not to inquire about health messages type and frequencies from participants.

Study Variables

Where possible, data were collected as continuous variables. Continuous variables were converted to categorical variables during the analysis phase where necessary. Information was collected relating to socio-demographics (address, age, formal education, employment, nature of job), cigarette smoking (current smoker, ex-smoker, number of cigarette smoked per day), use of smokeless tobacco (chewable tobacco, naswar), physical activity (vigorous physical activity, moderate physical activity, leisure time activities, household activities), leisure time physical activity, dietary habits (frequency of consumption of major foods, especially consumption of dietary fat), anthropometric measurements (height, weight), co-morbidities (including HTN, DM, angina pectoris), family history of CAD, body mass index (BMI), anxiety, depression and general health, using a tailored questionnaire designed specifically for the purpose of the study (food frequency questionnaire), and international validated questionnaire (International Physical Activity Questionnaire [IPAQ] short version (spearman correlation coefficient range = 0.42 to 0.43, and intra-class correlation ranged from 0.56 to 0.68) [189], Patients Health Questionnaire [PHQ9] (sensitivity = 75%, Specificity = 90%) for depression [159], and Generalized Anxiety Disorder [GAD7] (sensitivity = 83 %, specificity = 46%) [160]. The questionnaires are available in supplementary section online.

Baseline Data Collection

Patients were approached by research assistants (RAs) during their inpatient stay for enrolment into the study. Data derived from and collected for this study were not made available to the patients' physicians. The study data were collected from June 2012 to

December 2013. A detailed questionnaire was developed in English, translated into Urdu by a certified translator, then back into English to ensure accuracy and to maintain the essence of the questions. Trained RAs administered the structured questionnaire to each participant at baseline. The questionnaire was designed to collect information relating to socio-demographics, health status, family history and CAD risk profile. Physical activity levels were assessed using a short version of the IPAQ and household activity portion of a leisure-time physical activities (LTPA) questionnaire of the Minnesota heart health program [100, 101]. As defined in IPAQ, three levels of physical activities were assessed. Daily walk is defined as walking at work and at home, walking to and travel from place to place, and any other walking individual might do solely for recreation, sport, exercise or leisure; moderate physical activities were activities that take moderate physical effort and make individual breathe somewhat harder than normal, like, carrying light weight; vigorous physical activities were activities that take hard physical effort and make individual breathe much harder than normal, like, heavy lifting. Depression and Anxiety were evaluated by PHQ 9 (Urdu version) and GAD 7 (Urdu version) questionnaires [102].

RAs were provided with extensive training by the principal investigator (JI) on how to frame each question and measure height, weight, heart rate, and blood pressure. An experienced laboratory technician drew venous blood samples from subjects following a 12-hour overnight fast. The blood samples were sent to the laboratory (Dr. Essa's Laboratory and diagnostic center, Karachi, Pakistan) for lipid profile and HbA1c.

Follow-Up Data Collection

The first follow-up was made at least six months (range: 180 days – 400 days) following enrolment. Subsequent follow-ups occurred on an average of 90 days' intervals. At each visit, blood tests were performed and questionnaire was administered.

Ethical Considerations

Ethics approval for the study was granted by the Human Ethics Review Board of Macquarie University. Approvals were also obtained from the institutional review boards of each participating hospital. A detailed consent form was developed for the patients explaining the objectives of the study and their rights. The informed consent form was drafted in English, translated into Urdu by certified translators, then back into English to ensure accuracy. At enrollment, participants were asked to read the informed consent form or it was read to them if they had difficulty in reading. Participants were encouraged to ask questions for clarification and were told that their participation was voluntary, and that they could withdraw at any time during the study.

Statistical methods

Intention to treat was the primary approach for the analysis. Allowances were made for attrition in the sample size estimation, but analyses were performed on the data with and without missing values.

Baseline characteristics of patients, those who died, and those who survived at the end of the study data collection, in intervention and non-intervention groups were analyzed using chi-square test (categorical variables) and t-test (continuous variables). The status (died or survived) of all subjects was assessed every six months over the course of the study. Cumulative survival was estimated using the Kaplan-Meier method, focused on the time interval with adequate follow-up. The time to death was calculated by determining the number of days from randomization for intervention to exact date the patient died. Censoring occurred for the primary outcome (mortality), losses to follow up, and those reaching the end of follow-up. Univariate and multivariable Cox-proportional hazard regressions were performed to examine the impact of intervention and mortality. Variables were chosen based on biological plausibility, postulated associations, on univariate exploratory analysis ($p = \leq 0.25$). For all

analyses, a probability value of less than 0.05 (two tailed) was significant. Means are represented with standard deviations, and hazard ratios are presented with 95% confidence interval (CI). Statistics were performed using IBM® SPSS® statistics software (v 21, IBM Corporation, USA)

RESULT:

A total of 2656 patients and 559 caregivers were enrolled between June 2012 to December 2013. Mean first follow-up period was 154 days (± SD 100), second follow-up period was 273 days (± SD 89) from baseline, and 3rd follow-up period was 329 days (± SD 70) from baseline. There were 86 (3.2%) deaths in total among patients, 41 deaths in intervention and 45 deaths in the non-intervention group, over the course of the study (table 1).

Comparison of socio-demographic, medical, and physical characteristics

Table 1a and 1b compares the results obtained from the preliminary analysis of socio-demographic and baseline characteristics of patients who died and those who survived over the course of the study data collection (referred as 'survived'). There were no statistically significant differences for major characteristics among dead and survived patients of the intervention group (see table 1). Whereas in non-intervention group there were statistically significant differences for some characteristics between dead and survived patients. Majority of the patients who died had no formal education (p = .003), the highest formal education reported was "high school (HSc.)" (p = .04), majority were unemployed (p = .002), majority of those who replied in affirmative for employment did not revealed their occupation (p = .002), and nature of job (p = .003). Table 1b report that the patients who died in comparison with survived patients in the intervention group were older in age (p = .025), had higher fasting and random blood sugar levels (p =.002, and .005 respectively). Among patients from the non-intervention group who died in comparison with survived patients were older in age (p =.001),

had lower levels of hemoglobin (p =.01), had higher serum creatinine levels (p =.04), and spend more time sitting on weekdays (p =.003).

Comparison of major risk factors between intervention and non-intervention groups of patients at baseline and first follow-up shows that there was a significant reduction in the serum cholesterol and LDL levels (p = .04 and p = .04 respectively) of intervention group as compared to non-intervention group from baseline to first follow-up. There was no change in other major risk factors measured in our RCT between intervention and non-intervention group from baseline to first follow-up (refer table 1d and 1e for detail).

Table 1a: Chi square test to compare proportion of death in intervention and Non-intervention group in Patients

Variable	Intervention Group n (%)	Non-intervention Group n (%)	df	*p*
Alive	1311 (97)	1259 (96.5)	1	.62
Dead	0041 (03.0)	0045 (03.5)		

Table 1b: Comparison of baseline characteristics of patients who died and survived in intervention and non-intervention group.

Variables	Intervention		P* Value	Non-Intervention		P value
	Alive n (%)	Dead n (%)		Alive n (%)	Dead n (%)	
Male	859 (97)	027 (3)	1.0	814 (97.1)	024 (2.9)	.16
Female	446 (97)	014 (3)		445 (95.5)	021 (4.5)	
Marital Status			.051			.76
Married	1277 (97.1)	038 (2.9)		1227 (96.5)	045 (3.5)	
Never Married	011 (84.6)	002 (15.4)		015 (100)	0 (0)	
Separated/divorced	009 (100)	00 (0)		009 (100)	0 (0)	
No Answer	014 (93.3)	1 (6.7)		008 (100)	0 (0)	
Ethnicity			.23			.86
Mohajir	805 (96.2)	032 (3.8)		744 (96.6)	26 (3.4)	
Punjabi	147 (98.2)	002 (1.3)		168 (96)	07 (4)	
Sindhi	057 (100)	0 (0)		057 (95)	03 (5)	
Balochi	023 (95.8)	001 (4.2)		13 (100)	0 (0)	
Pushto	112 (99.1)	001 (0.9)		111 (95.7)	05 (4.3)	
Other	167 (97.1)	005 (2.9)		166 (97.6)	04 (2.4)	
Formal Education			.10			.003
Yes	570 (96.9)	18 (3.1)		523 (98.3)	9 (1.7)	
No	635 (97.5)	16 (2.5)		628 (94.9)	34 (5.1)	
No Ans.	106 (93.8)	07 (6.2)		108 (98.2)	02 (1.8)	
Level of Education			.50			.04
Primary	130 (98.5)	2 (4.9)		121 (96.8)	4 (3.2)	
Secondary	218 (94.8)	12 (29.3)		215 (99.5)	1 (0.5)	
HSC	067 (98.5)	1 (2.4)		053 (94.6)	3 (5.4)	
Bachelors	091 (97.8)	2 (4.9)		081 (100)	0 (0)	
Masters	022 (100)	0		022 (100)	0 (0)	
PhD	001 (100)	0		002 (100)	0 (0)	
MBBS	003 (100)	0		0 (0)	0 (0)	
Missing	779 (97)	24 (3)		765 (95.4)	37 (4.6)	

* Chi Square test to compare the proportion of dichotomous variables (baseline characteristics of survived and deed patients in intervention and non-intervention group

Table 1c: t-test for the Comparison of mean of basic characteristic of patients (between dead and survived at end of study) in intervention and non-intervention groups.

Variable	Intervention Group				p	Non-intervention Group				P
	Survived		Dead			Survived		Dead		
	n	mean (± SD)	n	mean (± SD)		n	mean (± SD)	n	mean (± SD)	
Age (Years)	1311	52.18 (10.3)	41	55.83 (10.21)	.02	1259	51.93 (10.27)	45	58.13 (9.41)	.00
Systolic Blood Pressure	1311	128.34 (23.4)	41	123.90 (23.10)	.23	1259	128.36 (23.98)	45	127.71 (25.63)	.86
Diastolic Blood Pressure	1309	77.96 (13.41)	41	74.10 (12.10)	.07	1258	78.47 (13.88)	45	79.36 (14.43)	.67
No. Cigarette smoke/day	61	20.11 (21.15)	04	4.25 (4.03)	.14	50	18.54 (17.56)	07	18.29 (12.24)	.97
Hemoglobin (g/dl)	766	12.80 (2.01)	31	12.26 (1.91)	.17	718	12.62 (1.94)	30	11.74 (2.14)	.01
Fasting Blood Sugar (mg/dl)	87	133.34 (82.29)	08	230.38 (99.77)	.00	103	160.64 (102)	06	152.33 (105)	.85
Random Blood Sugar (mg/dl)	602	174.54 (92.05)	21	269.38 (136.8)	.00	546	175.82 (99.73)	23	215 (131)	.07
Serum Creatinine (mg/dl)	787	1.17 (0.72)	32	1.23 (0.25)	.64	723	1.23 (1.16)	30	2.06 (2.07)	.04
Vigorous physical activities (VPA)/day	195	3.71 (2.32)	04	4.25 (3.20)	.64	195	3.82 (2.46)	03	4.67 (3.21)	.55
VPA (Time) in minutes	195	162.55 (154.1)	04	130 (118.32)	.67	195	178.65 (167)	03	120 (60)	.55
VPA/Week (minutes)	194	857 (1248)	04	825 (906.47)	.96	193	1123 (1969)	03	780 (334.06)	.76
Moderate physical activities (MPA)/day	545	5.60 (1.57)	13	5.31 (2.32)	.52	522	5.41 (1.75)	13	6 (1.63)	.23
MPA (Time) in minutes	545	226.30 (196.6)	13	163.85 (185.18	.26	522	213.88 (194.1)	13	159.23 (192.24)	.32
MPA/Week (minutes)	541	1214 (1260)	13	(1007.08)	.56	518	1216 (1267.7)	13	861 (1118.37)	.32
Daily Walk (minutes)	519	38.40 (47.02)	10	51.50 (41.03)	.39	444	38.5 (49.67)	14	27.14 (16.13)	.39
Daily Walk/week (minutes)	515	269 (567)	10	736 (1520)	.36	435	269 (486)	14	149 (108)	.36
Sitting Time (minutes)	1311	405.12 (182.7)	41	393.66 (215.4)	.69	1259	402.46 (186.7)	45	488 (191.71)	.00
PHQ 9 at baseline	1103	3.94 (3.76)	33	5.06 (4.16)	.48	1259	4.24 (4.26)	45	4.31 (3.05)	.74
GAD7 at baseline	1103	3.94 (3.76)	33	4.15 (3.42)	.75	1259	3.72 (3.48)	45	3.78 (2.89)	.90

Table 1d: t- test to compare major risk factors between intervention and non-intervention groups of patients at baseline and at first follow up

Patients: Baseline assessment						**Patients: Follow-up assessment**				
Variables	**Intervention M (± SD)**	**Non-Intervention M (± SD)**	**t**	**P**	**95% C.I.**	**Intervention M ..(± SD)**	**Non-Intervention M (± SD)**	**t**	**P**	**95% C.I.**
Systolic Blood Pressure	128 (23.38)	128 (24.20)	-.15	.88	-1.95 – 1.66	132 (22.14)	133 (21.28)	-.39	.70	-7.64 – 5.10
Diastolic Blood Pressure	77.83 (13.39)	78.50 (13.89)	-1.26	.20	-1.70 - .37	77.50 (12.91)	77.24 (12.48)	.13	.90	-3.49 – 3.97
No. of cigarette smoke/day	19.14 (20.86)	18.51 (16.91)	.18	.86	-6.24 – 7.50	16.86 (16.07)	14.76 (12.35)	.87	.38	-2.66 – 6.87
Vigorous physical activity/day/minutes	161.90 (153.32)	177.80 (166.83)	-.99	.32	-47.48 – 15.75	192.14 (204.88)	187.50 (178.49)	.07	.94	-126.06 – 135.34
Walk/day/week	5.96 (1.45)	5.74 (1.70)	2.19	.03	.02 - .42	3.26 (4.10)	3.22 (7.11)	.15	.87	-.52 - .61
Walk/day/minutes	38.58 (46.90)	38.20 (49.02)	.12	.90	-5.62 – 6.38	29.12 (44.42)	30.52 (50.52)	-.40	.68	-8.14 – 5.34
Walk/week/minutes	277.82 (599.19)	264.90 (478.73)	.36	.71	-56.07 – 81.92	193.22 (313.33)	187.52 (266.99)	.27	.78	-35.82 – 47.22
Sitting/day/minutes	404.92 (182.78)	405.41 (187.49)	-.07	.94	-14.58 – 13.60	283.83 (618.52)	268.96 (213.27)	.64	.52	-30.38 – 60.12
Serum Cholesterol	174.47 (33.87)	172.03 (35.72)	.83	.41	-3.36 – 8.25	157.75 (29.98)	182.60 (83.04)	-2.04	.04	-49.05 - -.64
HDL	42.37 (4.30)	42.26 (4.66)	.29	.77	-.64 - .86	43.31 (3.08)	41.78 (5.75)	1.72	.09	-.24 – 3.29
LDL	100.76 (31.36)	98.79 (35.20)	.69	.48	-3.60 – 7.54	89.06 (26.60)	103.44 (43.05)	-2.09	.04	-28.04 - -.72
VLDL	31.50 (17.83)	31.19 (17.58)	.20	.83	-2.64 – 3.26	26.02 (11.58)	37.24 (58.38)	-1.39	.17	-27.30 – 4.86
Triglycerides	158.90 (90.69)	155.33 (87.99)	.47	.63	-11.33 – 18.47	130.62 (57.72)	184.56 (292.87)	-1.34	.18	-134.60 – 26.70
Total lipids	823.47 (120.03)	815.79 (116.94)	.76	.44	-12.08 – 27.43	768.71 (93.13)	856.29 (390.52)	-1.57	.12	-197.83 – 22.68
Cholesterol, HDl ratio	4.32 (1.28)	4.20 (1.47)	.32	.75	-.20 - .27	3.75 (.98)	4.70 (3.90)	-1.70	.09	-2.05 - .16
HbA1C	6.71 (1.86)	6.70 (1.77)	.12	.89	-.28 - .32	6.24 (1.44)	6.37 (1.81)	-.41	.68	-.76 - .50

M = mean, **SD** = Standard Deviation, **t** = t statistics, **95% C.I**. = 95% confidence interval,

Table 1e: Chi square test to compare major risk factors between intervention and non-intervention groups of patients at baseline and at first follow up

Patients: Baseline assessment				**Patients: Follow-up assessment**		
Variables	**Intervention n (%)**	**Non-Intervention n (%)**	**p**	**Intervention n (%)**	**Non-Intervention n (%)**	**P**
Smoking Tobacco			.25			1.00
Yes	307 (22.7)	305 (23.4)		107 (13.2)	107 (13.3)	
No	103 (76.2)	992 (76.1)		706 (86.8)	699 (86.7)	
No Answer	015 (1.1)	007 (0.5)		00 (0)	00 (0)	
Ex-Smoker			.75			.84
Yes	0071 (5.4)	0065 (5.1)		098 (12.3)	101 (12.8)	
No	1236 (94.6)	1215 (94.9)		697 (87.7)	688 (87.2)	
Chest Pain (self-reported)			.18			.15
Yes	560 (44.6)	510 (42)		251 (41.6)	226 (37.4)	
No	696 (55.4)	708 (58)		353 (58.4)	376 (62.6)	
Extra salt (on food)			1.00			.52
Yes	0223 (16.5)	0214 (16.4)		021 (2.6)	016 (2.0)	
No	1130 (83.5)	1090 (83.6)		792 (97.4)	790 (98)	

Kaplan-Meier survival analysis:

Kaplan-Meier estimator was used to explore the variables that usually recognized as influencing survival for CAD patients. Statistically significant differences between the survival curves of selected covariate in intervention and non-intervention group were calculated by log-rank test.

The estimated mean time until death was 534 days for intervention group and 514 days for non-intervention group. As the p-value (.21) is greater than .05, conclude that there is no significant evidence of a difference in survival times for patients in intervention and non-intervention groups. The covariate most likely associated with the survival time in days were investigated using Kaplan-Meier estimator (see table 2a)

There is significant evidence of a difference in survival times for diabetics (p = .001), those who are not employed (p = .032), having anterior wall MI (p = .001), and having ST elevated MI (p = .028), in patients of intervention group. There was significant difference in survival

time for not employed (p = .001), not diagnosed MI (p = .05), and history of hypertension (p = .001), in patients of non-intervention group (see table 2b).

Table 2a: Kaplan Meier analysis to report time to event (survival time) of patients in intervention and non-intervention group.

Variables	n	Number of events (Deaths)	Number censored n (%)	Mean survival time in days (95% CI.)	P
Intervention Group	1349	41	1308 (97.0)	534 (516.80 – 550.60)	.21
Non-Intervention Group	1305	45	1260 (96.6)	514 (505.07 – 522.63)	

Fig. 1: Survival plot to show survival probability for intervention and non-intervention group

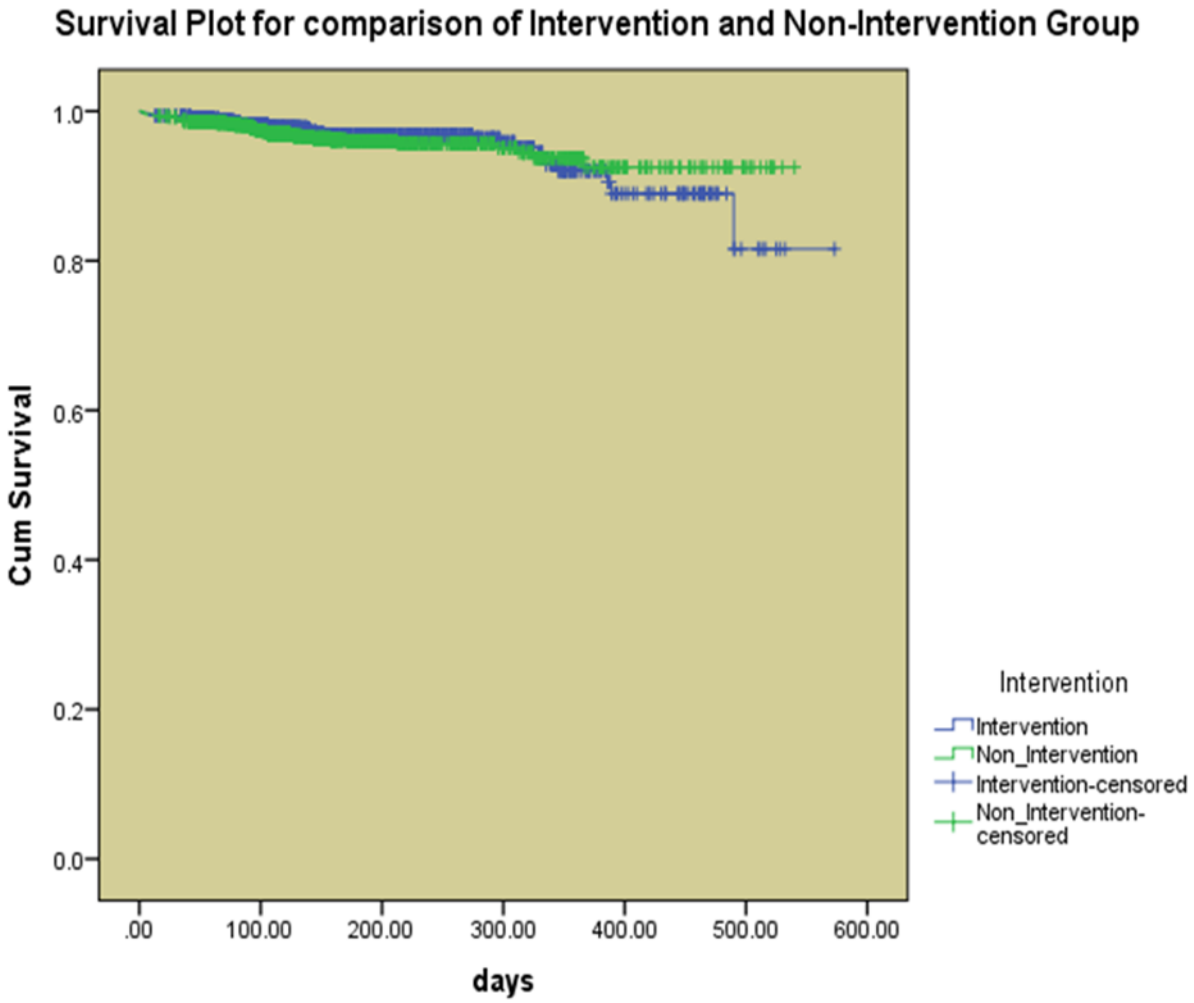


Table 2b: Kaplan Meier survival analysis for survived and dead intervention and non-intervention group of CAD patients

Variables	n	Number of events Deaths n (%)	Number censored n (%)	Mean survival time in days (95% CI.)	P
Intervention					.65
Male	890	27 (3)	863 (97)	499.28 (484 .15 – 514.40)	
Female	459	14 (3)	445 (97)	536.19 (510.39 – 561.99)	
Non-Intervention					.13
Male	838	24 (2.9)	814 (97.1)	501.17 (491.21 – 511.13)	
Female	467	21 (4.5)	446 (95.5)	508.73 (493.72 – 523.73)	
Intervention					.56
Age ≤ 40 yrs.	198	04 (02)	194 (98)	499.64 (483.49 – 515.80)	
Age > 40 yrs.	1151	37 (3.20)	1114 (96.80)	535.40 (520.63 – 550.17)	
Non-Intervention					.19
Age ≤ 40 yrs.	176	03 (1.7)	173 (98.30)	520.73 (510.33 – 531.14)	
Age > 40 yrs.	1129	42 (3.72)	1087 (96.28)	511.34 (501.38 – 521.29)	
Intervention					.99
Smoking cigarette (Y)	306	08 (2.6)	298 (97.4)	512.06 (497.10 – 527.03)	
Smoking cigarette (N)	1043	33 (3.2)	1010 (96.8)	525.25 (501.02 – 549.48)	
Non-Intervention					.06
Smoking cigarette (Y)	305	07 (2.3)	298 (97.7)	501.50 (484.28 – 518.72)	
Smoking cigarette (N)	1000	38 (3.8)	962 (96.2)	514.19 (505.36 – 523.03)	
Intervention					.18
Myocardial Infarction. (Y)	536	24 (4.5)	512 (95.5)	479.98 (464.67 – 495.29)	
Myocardial Infarction. (N)	324	08 (2.5)	316 (97.5)	509.52 (495.85 – 523.18)	
Non-Intervention					.05
Myocardial Infarction. (Y)	551	26 (4.7)	525 (95.3)	506.54 (492.80 – 520.29)	
Myocardial Infarction. (N)	318	06 (1.9)	312 (98.1)	516.45 (504.02 – 528.88)	
Intervention					.001
Anterior Wall MI. (Y)	123	09 (6.3)	114 (92.7)	473.55 (445.83 – 501.27)	
Anterior Wall MI. (N)	473	16 (3.4)	451 (96.6)	491.50 (473.76 – 509.25)	
Non-Intervention					.25
Anterior Wall MI. (Y)	152	09 (5.9)	143 (94.1)	485.33 (460.16 –510.51)	
Anterior Wall MI. (N)	444	17 (3.8)	427 (96.2)	511.22 (495.92 – 526.51)	
Intervention					.02
ST Elevated MI	063	06 (9.5)	057 (90.5)	422.30 (385.15 – 459.46)	
Non ST Elevated MI	231	12 (5.2)	219 (94.8)	456.20 (434.46 – 477.95)	
Non-Intervention					.26
ST Elevated MI	068	03 (4.4)	65 (95.6)	498.67 (471.74 - 525.60)	
Non ST Elevated MI	226	17 (7.5)	209 (92.5)	486.59 (458.76 - 514.41)	
Intervention					.52
Family Med. H. (Y)	460	14 (3)	446 (97)	503.29 (486.73 – 519.85)	
Family Med. H. (N)	857	26 (3)	831 (97)	528.72 (501.73 – 555.70)	
Non-Intervention					.11
Family Med History. (Y)	418	11 (2.6)	407 (97.4)	523.28 (512.93 – 533.63)	
Family Med. History. (N)	856	33 (3.9)	823 (96.1)	498.65 (485.73 – 511.56)	
Intervention					.07
Hypertension (Y)	762	29 (3.8)	733 (96.2)	527.79 (503.44 – 552.13)	
Hypertension (N)	582	12 (02)	575 (98)	505.77 (488.78 – 522.76)	
Non-Intervention					.001
Hypertension (Y)	741	37 (05)	704 (95)	481.62 (468.65 – 494.60)	
Hypertension (N)	564	08 (1.4)	556 (98.6)	529.26 (520.80 – 537.71)	

Table 2b (cont.): Kaplan Meier survival analysis for, remain alive and dead patients at the end of study, in intervention and non-intervention group of CAD patients

Variables	n	Number of events (Deaths)	Number censored n (%)	Mean survival time in days (95% CI.)	P
Intervention					
Systolic BP (≤ 120 mmHg)	654	22 (3.4)	632 (96.6)	495.76 (477.66 – 513.87)	.57
Systolic BP. (>120 mmHg	695	19 (2.7)	676 (97.3)	541.31 (523.28 – 559.33)	
Non-Intervention					
Systolic BP (≤ 120 mmHg)	638	22 (3.4)	616 (96.6)	511.60 (497.15 – 526.06)	.97
Systolic BP. (>120 mmHg	667	23 (3.4)	644 (96.6)	506.48 (496.30 – 516.68)	
Intervention					
Diastolic BP (≤ 90 mmHg)	1215	39 (3.8)	117 (96.8)	531.51 (513.88 – 549.14)	.36
Diastolic BP. (> 90 mmHg)	132	02 (1.5)	130 (98.5)	453.15 (442.25 – 464.05)	
Non-Intervention					
Diastolic BP (≤ 90 mmHg)	1182	39 (3.3)	1143 (96.7)	514.86 (505.80 – 523.92)	.28
Diastolic BP. (> 90 mmHg)	0122	06 (4.9)	0116 (95.1)	453.92 (430.79 - 477.05)	
Intervention					.001
Diabetes M. (Y)	450	26 (5.8)	424 (94.2)	514.28 (487.69 – 540.87)	
Diabetes M. (N)	899	15 (1.7)	884 (98.3)	511.91 (499.65 – 524.17)	
Non-Intervention					.36
Diabetes M. (Y)	429	18 (4.2)	411 (95.8)	492.22 (470.74 – 513.70)	
Diabetes M. (N	876	27 (3)	849 (97)	519.26 (511.01 – 527.51)	
Intervention					.032
Employed (Y)	619	13 (2.1)	606 (97.9)	500.53 (485.24 – 515.82)	
Employed (N)	730	28 (3.8)	702 (96.2)	531.64 (512.82 – 550.47)	
Non-Intervention					.001
Employed (Y)	589	08 (1.4)	581 (98.6)	495.58 (490.42 – 500.74)	
Employed (N)	715	37 (5.2)	678 (94.8)	498.12 (482.40 – 513.83)	
Intervention					.17
Total Cholesterol (≤ 200 mg/dl)	214	17 (7.9)	197 (92.1)	476 .54 (452.98 – 500.11)	
Total Cholesterol (> 200 mg/dl)	058	02 (3.4)	056 (96.6)	449.587 (429.98 – 469.19)	
Non-Intervention					.99
Total Cholesterol (≤ 200 mg/dl)	237	06 (2.5)	231 (97.5)	515.82 (504.46 – 527.18)	
Total Cholesterol (> 200 mg/dl	045	01 (2.2)	044 (97.8)	453.16 (436.09 – 470.24)	
Intervention					.14
VLDL (≤ 30 mg/dl)	159	14 (8.8)	145 (91.2)	458.77 (433.29 – 484.25)	
VLDL. (> 30 mg/dl)	113	05 (4.4)	108 (95.6)	502.23 (479.11 – 525.35)	
Non-Intervention					.51
VLDL (≤ 30 mg/dl)	171	04 (2.3)	167 (97.7)	507.36 (494.03 – 520.69)	
VLDL. (> 30 mg/dl)	111	03 (2.7)	108 (97.3)	517.05 (502.57 – 531.53)	
Intervention					.11
Triglyceride (≤ 150 mg/dl)	153	14 (9.2)	139 (90.8)	457.48 (431.49 – 483.46)	
Triglyceride (> 150 mg/dl)	119	05 (4.2)	114 (95.8)	502.80 (480.02 – 525.58)	
Non-Intervention					.33
Triglyceride (≤ 150 mg/dl)	171	03 (1.8)	168 (98.2)	511.41 (500.47 – 522.35)	
Triglyceride (> 150 mg/dl)	111	04 (3.6)	107 (96.4)	510.18 (490.75 – 529.63)	
Intervention					.17
PHQ9 (mean = (≤ 10)	1191	35 (2.9)	1156 (97.1)	539.93 (526.83 – 553.04)	
PHQ9 (mean = (> 10)	0158	06(3.8)	0152 (96.2)	474.42 (459.70 – 489.16)	
Non-Intervention					.29
PHQ9 (mean = (≤ 10)	1172	43 (3.7)	1129 (96.3)	512.83 (503.66 – 522.00)	
PHQ9 (mean = (> 10)	0133	02 (1.5)	0131 (98.5)	386.51 (376.27 – 396.75)	

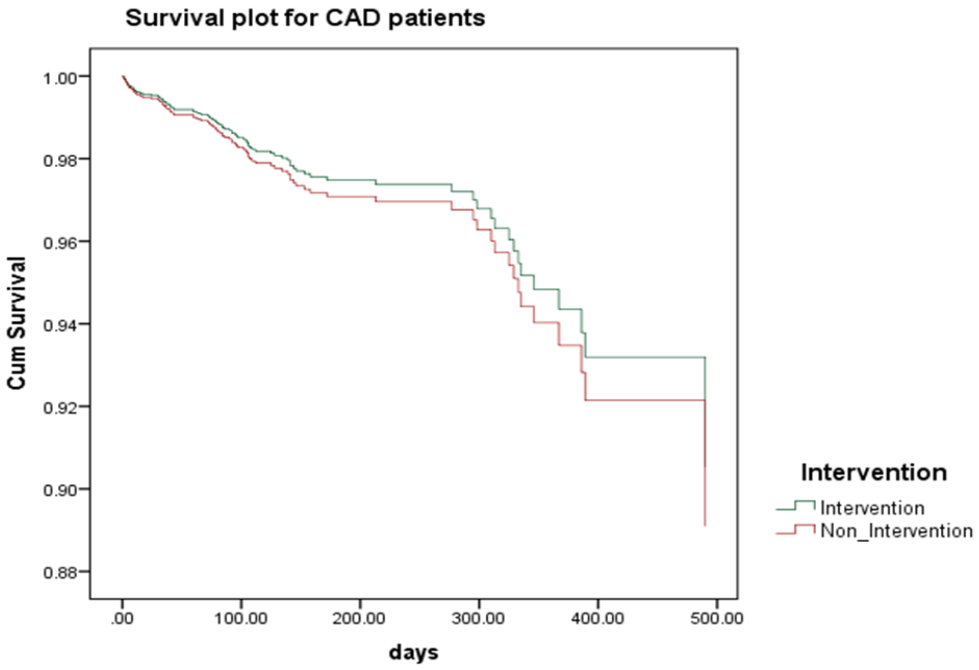
Cox-Proportional Hazards Regression:

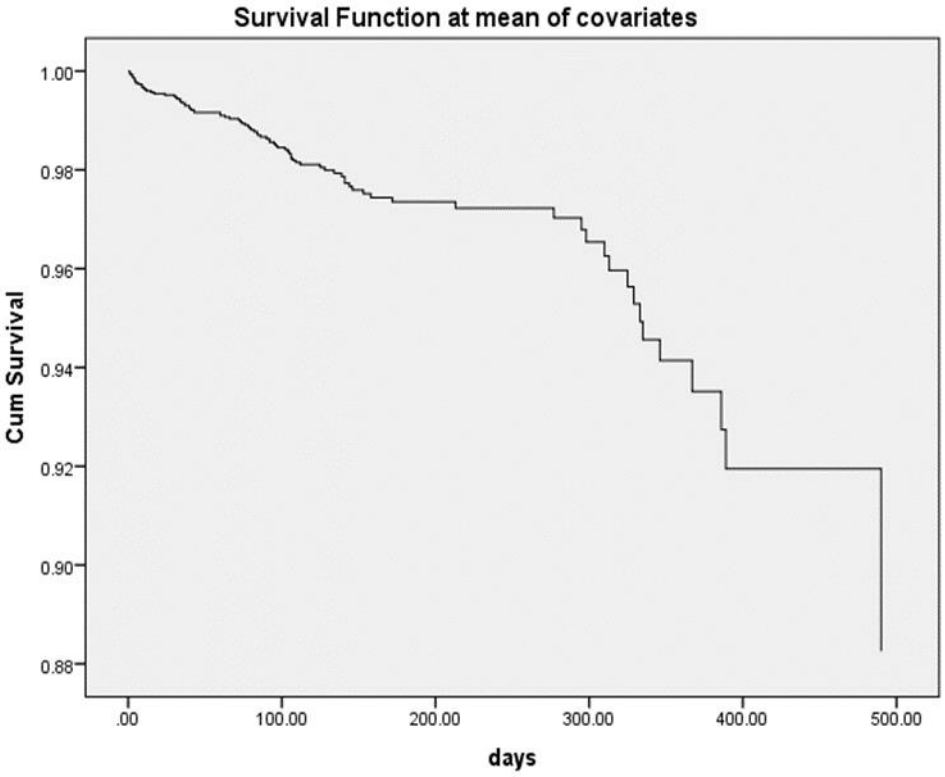
We performed cox regression to compares the hazard of the intervention and non-intervention groups and allowed several variables to be taken into account. Based on a final multivariable Cox regression model, for age (p = .002), for an each addition year increase in age the hazard increases by 4 percent, for employed (p = .010), those who are employed the hazard decrease by 51%, being diabetic (p = .020), for those who were diabetic, the hazard increase by 68%, or the hazard for diabetic is 1.68 times that of non-diabetic, for hypertensive (p = .020), the hazard for hypertensive is 1.92 times that of non-hypertensive or hazard increase by 92% for hypertensive. The variables are significant after controlling all other variables in the model (see table 3).

Table 3: Cox-Proportional Hazard Regression: Unadjusted and adjusted hazard ratio of CAD

Variables	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p
Intervention (Yes)	1.13 (0.74 - 1.72)	.58	1.18 (0.77, 1.81)	.44
Gender (Female)	0.78 (0.51 - 1.20)	.27	1.53 (0.91, 2.56)	.11
Age (years)	1.05 (1.03 - 1.07)	.001	1.04 (1.01, 1.06)	.002
Ethnicity (Mohajir) – Ref. Punjabi Sindhi Balochi Pushto No Ans.	 0.79 (0.39 – 1.60) 0.86 (0.27 – 2.76) 0.85 (0.12 – 6.14) 0.82 (0.36 – 1.92) 0.91 (0.45 – 1.84)	 .98 .51 .80 .87 .66 .79		
Formal Education (Yes) Ref. No No Ans.	 1.69 (1.06 – 2.71) 1.67 (0.79 – 3.56)	 .08 .03 .18		
Employed (Yes)	0.36 (0.22 – 0.60)	.001	0.49 (0.27 – 0.86)	.010
Nature of Job Desk Job Laborer (Physical) Mix	 2.90 (1.03 – 8.15) 0.97 (0.36 – 2.60)	 .80 .04 .95		
Diabetes Mellitus (No)	2.09 (1.37 – 3.19)	.001	1.68 (1.08 – 2.60)	.020
Hypertension (No)	2.46 (1.49 – 4.05)	.001	1.92 (1.13 – 3.26)	.020
Smoking (No)	0.67 (0.38 – 1.16)	.15		
Chest Pain (No)	0.99 (0.46 – 2.15)	.98		
Myocardial Infarction(MI) (No)	1.97 (1.09 – 3.56)	.03		
Anterior Wall MI	1.87 (1.06 – 3.34)	.03		
Family History of CAD (No)	0.69 (0.43 – 1.10)	.11		
Consanguineous marriage of parents	0.89 (0.54 – 1.45)	.64		
Time spent sitting in week days (in minutes)	1.001 (1.000 – 1.002)	.01	1.001 (1.000 – 1.002)	.049
PHQ 9	1.03 (0.99 – 1.08)	.13	1.01 (0.94 – 1.07)	.84
GAD7	1.05 (0.99 – 1.11)	.10	1.05 (0.98 – 1.14)	.17

Fig. 2: Cox-proportional survival plot for selected covariates in final model.





DISCUSSION:

Our study explored the ability of mobile phone text messages (SMS) to reduce risk factors attributed to CAD, which in turn reduces mortality rate in newly diagnosed cardiac patients. The main finding of our research is that the mean survival time for intervention group and non-intervention group was not statistically different. Though there were numerically more deaths in the non-intervention group as compared to the intervention group, however, this difference was not statistically significant. During this study, our intervention (mobile phone text messaging to promote healthy lifestyle) was not effective in reducing the mortality in the intervention group as compared to the non-intervention (usual care group without intervention). Further analysis of our research suggests that old age at first event of CAD, unemployment, history of diabetes mellitus, history of hypertension, and major time spent in sitting on week days were found to be independently associated with mortality rate in CAD patients in Pakistan.

To our knowledge, this is the first study which explored the utility of phone text messaging to promote healthy lifestyle and its relation in reducing in first ever CAD patients in Pakistan. Our study reported total 86 deaths (3.2%) during the course of data collection (18 months). If we exclude those participants whom we did not had any contact during subsequent follow-up, e.g., wrong mobile numbers and phone constantly turned off, percentage only shifts from 3.2% to 4.2%. A possible explanation for low one-year mortality in our trial participants might be that SA suffer their first ever cardiac assault at an earlier age (compared with Western population), and young aged patients might be more capable of surviving a cardiac assault. There is a scarcity of valid mortality data from Pakistan [97, 190, 191], and to our knowledge, our study is one of very few studies in the Pakistan population, that report mortality rates among first ever CAD patients. One study conducted in Pakistan to determine the outcome of primary percutaneous intervention (PCI) reported that mortality rate was 7.9% during their six months' study period which comprised of 5.9% dying while still in hospital and a further 2% dying after six months' follow-up [192]. One-year retrospective review of death certificates and hospital

charts of patients dying on general and specialty medical services at one tertiary care hospital in Pakistan also show that mortality was lowest in cardiology (2.26%) [97]. Studies on a mortality rate in CAD patients, done on immigrants of SA in western countries have given conflicting results. The mortality rate reported in CAD patients of SA origin in Western countries ranges from 6.1% to 10%, and among native Caucasian population it ranged from 1.5% to 8% [193-197]. One study conducted in Canada to observe outcomes following percutaneous coronary intervention in SA and white patients showed that there was no significant difference in mortality within 30 days and 1 year between SA and Caucasian patients (3% versus 2.3%) [198]. One study found significantly higher 6 months' mortality rates in SA subjects than in Caucasian (Canadian) control subjects [95]. Whereas, two other studies did not report any significant difference up to 4 years after MI between SA and Caucasian subjects [195, 199]. In other Canadian studies SA had similar short term mortality but a lower long-term mortality compared with non-SA subjects [193, 194]. One study from Canada showed higher one year mortality among SA patients than non-SA patients (6.1% versus 1.5%), and there was a difference in the risk profile between SA and non-SA [200] . Recent large studies conducted in European region showed lower mortality among SA than non-SA subjects [197, 201]. One study conducted in Netherland based on nationwide registers from 1998 to 2010, for information regarding CAD/CHF hospitalization and outcome, showed 28 days' mortality was higher in SA than Dutch subjects, whereas 5 years' mortality rate was lower in SA than Dutch subjects [196]. Results of one recent study from UK based on the retrospective analysis of CAD patients between 2004 and 2009, reported 9% mortality among immigrant SA and 7.4% mortality among white indigenous sample [202].

The intervention component of our study aimed at promoting healthy lifestyle by targeting major risk factors attributable to CAD which would have indirect effect in reducing mortality among CAD patients. On the basis of baseline assessment of risk factors attributable to CAD

in our study patients, old age at first event of CAD, unemployment, history of diabetes mellitus, history of hypertension, and major time spent sitting on week days were found to be independently associated with mortality among CAD patients. Similar risk factors were also reported to be responsible for high mortality in CAD patients of SA immigrants in western countries. For example, a study observing difference between SA and white European in five-year outcome following percutaneous coronary intervention concluded that there was no long-term difference in all-cause mortality between SA and Caucasian European patients, despite SA having symptomatic CAD at a younger age and a higher prevalence of diabetes [203]. The explanation for high short term mortality in SA immigrants than native Caucasian European population showed, that a) SA had a higher degree of disease severity, b) high prevalence of comorbidity (particularly high prevalence of diabetes and hypertension), c) and concomitant cardiovascular risk factors [196].

Future Directions/recommendations for future research.

One of our study investigators (JI), who supervised data collection, conducted some in person discussions with the patients of the intervention group (around 25%) to keep an update on the compliance of patients in receiving, and reading SMS messages, and adopting a healthy lifestyle. The discussion revealed issues faced by majority of the participants participated in the discussion (also reported in print and electronic media). The main issues raised by the participants are as follows:

a) Participants appreciated our health message, and equally appreciated SMS service to deliver those messages. They agree that health messages did enhance their knowledge, and motivated them to adopt the positive lifestyle, however, their main issue was how to adopt in practice those positive lifestyle habits recommended by our text messages? For example, for our promotion for physical activity to adopt daily walk, the main issue raised by the participants was the safety, security and rule of law in the country, and

particularly in Karachi. The neighboring war in Afghanistan had a huge impact on Pakistan, in general, and Karachi in particular. The safety and security situation in Karachi was so bad that participants informed us that they only go out of their houses when it is absolute necessity, like on job, essential grocery shopping, etc. The other issue they raised was the scarcity of parks, and jogging track within their safe neighborhood also restrain them in adopting a daily walk, as promoted by our health messages

b) Even though many participants in the intervention group reported an increase in knowledge regarding healthy food, they also reported that their behaviours did not change because they could not afford to buy the healthy food. The bad economic situation, corruption and high inflation rate in Pakistan badly affected the income capacity and buying power of the general public. Many participants informed us that they have an extended family, and they can barely able to provide three meals a day to their families, and that too by mainly opting for low quality or unhealthy options (like unsealed saturated fat). Providing fresh fruits and vegetables regularly was beyond their means. Low buying power also had a negative impact on regular purchase of their prescribed medication.

The issues pointed out by the participants of our intervention group can be compared by the widely published report on safety and security situation [22, 164, 204, 205], low economic condition (recent World Bank report show that over 50% of Pakistan's population is living below the poverty line, less than $ 1.25 a day) [206], food poverty [207], low expenditure on health [149], and lack of provisions of health facilities for general public in Pakistan [149]. To associate the mentioned issues with the lack of healthy lifestyle behaviours need further exploration. The above-mentioned issues could have refrained a portion of motivated population of the society to adopt the healthy lifestyle; however, there are other, cultural and

related factors that can influence many other section of the population for not to adopt healthy lifestyle, Studies conducted in the western region on SA immigrants show that most SA know about positive lifestyle and healthy options but few adopt those healthy options [208, 209].

Strength and Limitations:

The major strength of our study is its sample size. To the best of our knowledge, this study is one of the largest CAD intervention studies conducted in Pakistan. Our study is probably the very first study conducted in Pakistan to explore the intervention of mobile phone text messages to promote healthy lifestyle in CAD patients.

The major limitation to acknowledge in our study is the rather high drop-out rate at follow-up. Despite our best effort to persuade our study participants to visit our study site for follow-up, only two thirds (66%) of the participants were able to complete the first follow-up. The main reason given by the participants was the prevailing rise of violence, and insecurity of life restraining them from engaging in undue travel. In addition, due to financial constraints, we were unable to continue offer free laboratory investigation to many of the participants, and we also did not have finances to compensate for the travel expenses at the first follow-up. The other limitation was that we only recruited the participants who survived (non-fatal) the initial hospitalization due to CAD, so we cannot comment on those who died while in hospital. Our study's follow-up was limited to an average of six months, which turned out to not be long enough to collect a sufficiently large sample of deceased participants. Almost all the participants died between baseline recruitment and first follow-up, thereby, we were unable to record their risk factor profile to observe the change, if any.

RECOMMONDATIONS

Within one-year mortality (short term) was 3.2% in our study participants, which is consistent with other published studies in the similar participants. Previous evidence has suggested that short-term and long mortality (5 years to 10 years) rate after CAD is not

significantly different between SA (including Pakistan) and western countries, and there is no definitive evidence that SA origin is an independent risk factor for the worst among in CAD patients. The main difference between SA and other western population is that SA suffer CAD at much younger and economically productive age, they have high prevalence of diabetes mellitus, and hypertension, and they are less physically active. In addition to other known risk factors, future studies should therefore specifically target these modifiable risk factors if intervening with CAD patients in Pakistan. Low follow-up rates, which inevitably increased our censored data, contributed to a major short coming of our study. Therefore, future studies in that area should ideally consider how to reduce the attrition rate. However, given the unique challenges in Pakistan that limit what can be done, researchers should also either carefully plan their sample size, or increase the attrition rate in sample size calculation.

The results of our study provide a probable explanation that any lifestyle modification interventions to prevent CAD will not be successful, unless there is a conducive environment provided by the government to adopt and afford the healthy lifestyle by every section of the community. Our study was probably the first study to explore the utility of affordable and far reachable media of mobile phone for the prevention of CAD in Pakistan. We, however, failed to prove the benefits of such an intervention. Future research in this area should also consider local political, environment, socio-demographic and cultural preferences in better designing the similar clinical trial in Pakistan. The present technological advancement in telecommunication in Pakistan (especially with the availability of latest 4 G technology) will increase the probability of success for the said intervention. One hypothesis could be generated from the failure of our solo text based intervention could be that the addition or combination of enhancements to text based intervention may produce positive results in promoting healthy lifestyle in CAD patients, and may be to healthy and young population. For example, enhancing SMS with MMS (for pictures, short video clip etc.) and where applicable web based

(internet) intervention. Other strategy could be a blended intervention of first face-to-face, a short term interaction at rehabilitation center (in order to develop some trust) and then a long term SMS based motivational and educational intervention. Future research design keeping an eye on the local situation like, security situation of the region like selecting secure environment where participants can move freely, and can adopt healthy-lifestyle, or developing motivational strategies and giving more practical solutions e.g., information on doing physical activity at home rather than going for walks in dangerous and less secure areas or where there are no parks, Utilization of well-known social media like Facebook, Skype, WhatsApp in combination with SMS can be a another strategy to enhance motivation, Perhaps using more social support e.g. groups getting together for discussion of management of diabetes or hypertension, or unemployment, etc., and then keep them motivated and in contact through SMS. Due to the high prevalence of premature CAD in Pakistani population than western populations, the very young population in Pakistan should be a main focus for future prevention studies.

Future researcher who would be interested in designing the similar clinical trial should also consider the low mortality within one year in CAD patients in Pakistan. To find some conclusive results on the effect of the said intervention (mobile phone text messaging for healthy lifestyle) on the reduction of mortality among CAD patients in Pakistan, researchers should aim to observe 3 to 5 years' mortality rates [195, 210, 211]. The probable explanation to adopt long term intervention in Pakistan could be lack of immediate acceptability for healthy options due to lack of education, affordability issue, and conducive environment to practice healthy option. Otherwise it has been shown in the western population (with high education rate, more stable economies, and provision of conducive environment by the governments) that mobile phone text messaging promotes positive lifestyle modification and disease prevention, including smoking cessation[104, 105], physical activity[106], weight management[107],

healthy diet[108], DM management[109, 110], and psychological wellbeing[107, 111], within 6 months to 18 months of intervention. A recent study by Chow et al from Australia concluded that intervention of mobile phone text messages for 6 months there was a modest improvement in LDL-C level, and greater reduction in systolic blood pressure, increase in physical activity, decrease in BMI, and cessation of cigarette smoking, among CAD patients who received intervention compared with usual care [72]. Given that there are limited prospects in increasing the funding for the prevention and rehabilitation programs and infrastructure to reduce the growing burden of CAD in Pakistan, progress will be highly dependent on finding opportunities for minimal new investment to spend on innovative strategies to reduce the burden and that could be incorporated in the existing health and development programs.

CONCLUSIONS

This study aimed to test the effectiveness of using SMS to change the 6-month mortality rates of CAD patients following their first cardiac event. The results of this study indicate that SMS may be ineffective in reducing mortality rates over one-year intervention to motivate individuals to adopt healthy lifestyle. However, the study did find that unemployment, history of diabetes and hypertension, and non-physical activity were independent risk factors for premature mortality over a 8 to 12 months follow-up. Future research should therefore particularly aim to target these modifiable risk factors in order to reduce mortality rates in CAD patients living in Pakistan. A study designed for 3 to 5 years' intervention may find some conclusive evidence for the effectiveness of SMS based intervention in Pakistan.

Competing interest:

No competing interest was declared by the authors.

Trial Registration:

The clinical trial is registered at Australia New Zealand Clinical Trial Registry (Reg. No: ACTRN12611000388910.)

Funding/Support:

The study was funded by a research grant from the Cardiac Health Institute, Sydney. Pathology studies were partially subsidized by Essa Diagnostic Laboratory, Pakistan

AUTHORS' CONTRIBUTION

Study Concept and Design:	Ismail
Protocol development and review:	Ismail, Kiat, Strodl, Ansari, Jun Ma
Macquarie University Ethics application:	Ismail, Kiat
Study sites approval & IRB:	Ismail, Kiat
Data collection and management:	Ismail
Drafting of the manuscript:	Ismail
Critical revision of the manuscript:	All authors
Statistical analysis:	Ismail, Strodl, Jun Ma
Obtained funding:	Kiat
Administrative, technical, or material support:	Ismail, Kiat, Ansari
Study Supervision:	Ismail, Kiat

ACKNOWLEDGMENT

We are thankful to all study participants to consent in the study and shared their experiences throughout the trial, as without their cooperation we would not have be able to get insight for our objectives. We acknowledge the contribution of our research assistants, Ms. Mehreen Aziz, Ms. Javeria Saeed, Ms. Yusra Iqbal, Ms. Safia, and Ms. in collecting the data

for the study. We are grateful for Essa Diagnostic Laboratory for providing the laboratory investigations on discounted rates. We appreciate the cooperation of all our participating study sites.

CHAPTER 5:

DISCUSSION

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DISCUSSION

Our randomized clinical trial explored the ability of mobile phone text messages to promote positive lifestyle (targeting major preventable risk factors associated with CAD), promote psychological wellbeing, in newly diagnosed cardiac patients and their primary caregivers, and to reduce mortality in patients' population. To the best of our knowledge our clinical trial stands out for its sample size, the intervention being conducted for the first time in Pakistan, and unique for its design to include primary care-givers of the patients in the study. Our randomized clinical trial resulted in enrolment of patients and their respective caregivers with comparative demographics between the intervention group (IG) population and the non-intervention group (NIG). The results of this clinical trial shows that there was no statistically significant difference in the mean scores of PHQ9 and GAD7 between intervention and non-intervention groups of patients and care givers. The result point out that our intervention did not achieved its intended object to promote psychological wellbeing more in intervention group than non-intervention group. This clinical trial also shows that the mean survival time for intervention group and non-intervention group was not statistically different. Though there were numerically more deaths in the non-intervention group as compared to the intervention group, but it did not have any statistically significance for the hazard ratio.

SIGNIFICANCE of the Study PROTOCOL

The majority of clinical trials on similar objectives have addressed only one or two cardiovascular risk factors [112-114]. Our clinical trial on other hand, examined the effect of mobile phone text messaging (SMS) on multiple cardiovascular risk factors, to promote positive behavior change intervention to newly diagnosed CAD patients and their care-givers.

To our knowledge, our clinical trial is the first in Asia to address the post cardiac event health management by SMS for the patients and their care-givers. The role of care givers and consequent adverse effect experienced by taking care of post event cardiac patient are well documented [54, 56] . A well informed care-giver is likely to be less stressed and psychosocially more stable, and more confident in taking care of their patients. This trial is also the first, to our knowledge, which addressed mortality as a primary outcome measure in the study of post cardiac event patient and their care-givers. To our knowledge our clinical trial is also first in promoting psychological wellbeing through SMS in CAD patients and their care-givers. The sample size of our clinical trial is also large enough to address all of the intended objectives.

BASELINE CHARACTERISTICS of STUDY SUBJECTS

The data from our study confirmed the high prevalence of modifiable risk factors among CAD patients in Pakistan. Majority of the patients were male and married, and nominated their spouse as their care-giver, therefore expectedly the mean age of the care-givers was younger than the patients (39 yrs. Vs 52 yrs.). The mean age of our study patients are consistent with recent studies from Pakistan and other SA countries, and was significantly lower than Western countries [99, 115-117]. Underscoring the more aggressive nature of CAD, in SA, which occurs at much younger age, and suffer 40% to 60% higher mortality than Caucasian population [6, 212, 213]Our study showed that 41% of the patients and 70% of the caregivers had any formal education, and 30% versus 60% had secondary and higher education, respectively. Previous studies from Pakistan showed 18 % of the cardiac patients and 42.4% of controls had tertiary education [99, 117]. Several studies from South Asia showed a higher CAD burden and prevalence of CVD risk factors among individuals with low levels of education [118-120]. Jaffrey et al [53] studied the cardiovascular health knowledge and behaviors in a large cohort of cardiac patients from tertiary care hospitals. The authors found that while 73% of the patients

had primary school education or higher striking, gaps existed in knowledge, particularly on the nature of CAD, its common symptoms and modifiable risk factors.

PREVALENCE of MODIFIABLE RISK FACTORS

- **Tobacco Smoking**

In our study Tobacco smoker comprised 23% (22.70% of IG and 23.40% of NIG) of the patients the prevalence of tobacco smokers in caregivers was only 9% (9.30% of IG and 8.60% of non-IG). The low prevalence of smokers among the caregivers may be due to gender difference, as majority of the participants were female in care-givers than in patients population, and there is low prevalence of cigarette smoking in female of SA countries [115]. Prevalence of smoking in the population of different SA countries was reported to be in between 21% and 72%, and around 28% among Pakistani population [121]. Whereas studies done in Pakistan showed that prevalence of smoking was in the range of 37% to 50% [116, 117]. A recent Australian mobile phone text messages intervention study among CAD patients shown that 53% of their participants were current smokers [72]. A meta-analysis of 13 studies involving heteronomous population cohorts from developed countries found SMS was overall efficacious in promoting smoking cessation [104].

- **Physical Activity**

In the present study, the baseline data showed, that 41% of patients were doing moderate physical activity for a mean of 5 days per week (almost same distribution in IG and NIG). Fifty-six percent of the caregivers were engaged in moderate physical activities for a mean of 6 days per week (57.3 % in IG and 55% in NIG). Thirty-seven percent of the patients walked on an average of 5.5 days per week, for an average of 38 minutes per day (39% in IG and 35% in NIG). Almost same walking pattern was observed in caregivers, but with a slight longer duration of walking time, on an average of 42 minutes per day. Average sedentary time spend by patients was 405 minutes (almost 7 hrs.) per day, whereas 393 minutes (6.5 hrs.) was spend

by caregivers. A study conducted in Karachi Pakistan to find out risk factors for CAD reported that 40% of the study subjects were engaged in regular physical activities [117]. Another study reported 4.3% of their study subjects were doing regular exercise [63]. Data from INTERHEART study showed that 4.6% of the study subjects from SA countries and 15.8% of study subjects from other countries were engaged in moderate to high intensity physical activities [115]. In comparison with published data from SA countries our study population showed that greater number of individuals were engaged in moderate to vigorous physical activities, which is quite surprising as it is mainly not consistent with other studies. This difference between studies results suggest that in recent years the rapid growth of digital media, and internet may have influenced our study subjects' attitude towards adopting positive lifestyle, or there may be an element of recall bias, which need to be explored further

- **Food Frequency**

Present study used food frequency questionnaire based on the local food items. The food choices of patients and their respective caregivers are quite similar due to the fact that they belong to the same family and share the same food, even then patients appeared to have preferences for healthier food. Caregivers appeared to outnumbered patients in consumption of sweets (64% vs 51%). Similar trend observed in potatoes consumption (94% of caregivers, 88% of patients), beef (caregivers 72%, patients 66%), soft drinks (caregivers 75%, patients 68%) ice cream (caregivers 64%, patients 47%), fruits (caregivers 92%, patients 87%), chocolates (caregivers 25%, patients 6%). More than 90% of the study subjects eat vegetables, beans/lentils and chicken, at least once per week. There was no major difference between patients and caregivers in the consumption of goat meat, egg white, salad, fresh fruit juices, bakery product, and plain rice. Studies from Karachi, Pakistan reported that 14% of their study subjects consumed fruits, 32% to 83% consumed red meat, and 37.8% to 72.7% use saturated fat in their cooking [99, 115, 117, 122]. The data from INTERHEART study showed that 20%

of CAD patients from SA countries consume fruits and vegetable as compared to 38.3% from other countries, whereas 26.5% of controls from SA and 45.2% from other countries consume fruits and vegetables[115]. Studies done on the relationship of diet and cardiovascular disease report that consumption of potato, red meat, and high intake of sodium was positively associated with the risk of developing CAD [123-125]. On the other hand, consumption of fruits and vegetables, dairy product, egg, rice, and dark chocolate are inversely related with the risk of CAD [126-132].

- **Depression and Anxiety**

Results from our study is consistent with data published from Pakistan and elsewhere [45, 133-135]. Our study implemented validated Urdu version of Patient Health Questionnaire (PHQ9) to evaluate depression, and Generalized Anxiety Disorder (GAD7) scale to evaluate baseline anxiety. PHQ9 and GAD7 have been used to evaluate depression and anxiety among CAD patients, and it has been validated in diverse cultural background [136-138]. The results of this study showed that 28.42% of the patients had moderate to severe depression (IG 28%, NIG 29%) at baseline assessment. Anxiety was present in 22.70% of patients (IG 22%, NIG 24%). Whereas, among caregivers' depression was acknowledged by approximately 25% of the participants (IG 29%, NIG 21%), and around 20% suffered from anxiety (IG 21%, NIG 25%). Study conducted in Saudi Arabian population showed that 31% patients visiting primary health care had mild and 13.4% had moderate depression [138]. Results from our study are in accord with previous studies indicating that prevalence of depression in CAD patients in Pakistan was reported to be in range of 27% to 37% [139, 140]. A clinical trial on three months effect of mobile internet based cognitive therapy on the course of depressive symptoms in remitted recurrently depressed patients reported that internet and text messages based cognitive therapy in patients with remission of depression is effective, however, it's long term effectiveness and replication to be evaluated further [141]. Systematic review of 13 studies,

mostly pilot studies with small sample, concluded that SMS text messaging may be an effective intervention for persons suffering from depression [142]. The authors indicated that larger randomized clinical trials are needed before recommendation can be done for implementation of specific depression SMS text messaging IG in primary care [142].

The present study showed that 33% of study patients, and 12% of caregivers had DM. HTN was prevalent in 56% of the patients and 31% of the caregivers. Studies done in Pakistan showed prevalence of DM from 22% to 30% in CAD patients [116, 117]. Analysis of INTERHEART study showed that 20.2% of the CAD patients and 9.5% of non-CAD subjects in SA countries had DM, and in comparison 18.2% of patients and 7.2% of their controls from other countries suffer from DM [115]. Study conducted in Pakistan to explore knowledge of CAD risk factors in CAD patients reported, that HTN was present in 43% of their study subjects [63]. WHO report on chronic diseases showed that prevalence of HTN was reported to be in the range of 30% to 40% in SA countries. Result from our study showed consistent results for the presence of DM, but HTN appeared to be more prevalent as compared to the previous local and regional data. High prevalence of HTN in Pakistani population may indicate that there may be not an effective preventive strategy or present strategies are not working. New effective strategies are to be explored to reduce the burden of HTN and DM.

Utility of Text Messages to promote Psychological Wellbeing

The results of our study found that majority of the patients in intervention and non-intervention groups were not depressed (63%). However, approximately 25% of the patients experienced mild symptoms of depression with approximately 12% experiencing moderate to severe depression at baseline. Similarly, approximately 21% of the CAD patients in this study reported mild levels of generalized anxiety, while 8% experienced moderate to severe levels of anxiety. The trend was almost similar at subsequent follow-ups. Female participants in this study experienced higher levels of depressive and anxious symptoms than male participants.

The prevalence rates of depression and anxiety from our study are consistent with similar studies conducted in Pakistan and other region of the world [165-167] one study conducted in Pakistan in CAD patients, reported that 27% of their study subjects were positive for depression on PHQ-9 scale [139]. A study conducted by Liang J. J. et al. in USA reported depression in 33% of cardiac patients, whereas, 37% suffered from anxiety [137]. Previous studies also confirmed that depression was more common and severe in females than males [140, 168-170]. Study conducted in USA reported that approximately 20% of their CAD patients were diagnosed with depression [171, 172]. Anxiety comorbid with depression increases mortality among CAD patients. A study conducted in USA reported that CAD patients' comorbid with anxiety symptoms showed two-fold increase in mortality [144]. A cross sectional study conducted in Saudi Arabia among primary care patients showed that 50% suffered from depression (majority 31% had mild depression)[138].

Among care-givers of our study, there was no significant difference between intervention and non-intervention groups in the prevalence of depression and anxiety at baseline. Among intervention 37% had mild to severe depression, whereas in non-intervention group 30% had mild to severe depression. Mild to severe GAD was prevalent in 29% of intervention group, and 22% had it in non-intervention group. Study conducted by Karin Oechsle et al. utilized GAD7 and PHQ9 to assess anxiety and depression in caregivers of terminally ill cancer patients[154]. The result of that study showed that 55% of the male and 36% of female caregivers were positive for moderate or severe anxiety, and 36% of the male caregivers as compared to 14% of the female caregivers suffered depression[154]. Caregivers' anxiety and depression were significantly correlated in their study. It has been reported that around 4% of the general population of USA suffered major depression in 2008[154]. Another study reported 76% of anxiety and 77% of depression among family caregivers of patients in palliative care[173]. One study conducted in three provincial capital cities of Pakistan reported regional

variation in the prevalence of depression; Lahore (53.4%), Quetta (49.3%), and Karachi (35.7%) [164]. That study explained the difference in the prevalence of depression in three different geographical areas as e attributed to local cultural influence, geographical locations, and social adversities.

The results from our study showed that our SMS based intervention did not have any effect in the reduction of depression and anxiety among our intervention group as compared to our non-intervention group in both CAD patients and caregivers. Although numerically there was a slight reduction in the mean scores of PHQ9 and GAD7 from baseline to follow-ups in both patient and caregivers, the trend was similar in intervention and non-intervention group, suggesting our intervention was not effective in significantly improving the psychological wellbeing of our intervention group. The potential explanation for our intervention not to achieve its' desired goal could be that text based messages are not convincing enough to promote psychological wellbeing. Secondly, the short duration of the intervention may have contributed in its failure. The study conducted by Agyapong et al. to observe the effective of their supportive mobile phone text messages to patients with depression and comorbid alcohol use disorder, 3 months after cessation of their intervention, did not find their intervention effective [174]. The explanation provided by the authors was that the effects of the intervention were not sustained beyond the period that the patients actually received the intervention [174]. The authors recommended long term intervention for the effect of the intervention to be sustainable [174]. Our study supported the findings of other studies, that female suffer more from anxiety and depression than male.

To the best of our knowledge this is the first study designed to utilize a mobile phone SMS based intervention for psychological wellbeing in CAD patients, and in particular the first to do so in a Pakistani population. As such it is difficult to directly compare our results with other studies. Few studies have shown successful results using telephone-delivered cognitive

behavioral therapy to depressed and anxious CAD patients [75, 175-181]. Though, telephone-delivered cognitive behavioral therapy is a different intervention compared to mobile phone text based psychological wellbeing, but both interventions could be combined for a long term benefit. As such there appears to be emerging evidence that SMS interventions alone may not be powerful enough to result in changes in depressive or anxious symptoms in CAD patients and caregivers, as well as the wider population

Utility of Text Messages to Reduce Mortality in CAD Patients

Though there were numerically more deaths in the non-intervention group as compared to the intervention group, but it did not have any statistically significance for the hazard ratio. During the study our intervention (text messaging (SMS) to promote healthy lifestyle) was not effective in reducing the mortality in the intervention group as compared to the non-intervention (usual care group without intervention). Further analysis of our research suggests that old age at first event of CAD, unemployment, history of diabetes mellitus, history of hypertension, and major time spent in sitting on week days were found to be independently associated with mortality rate in CAD patients in Pakistan.

To our knowledge, this is the first study which explored the utility of phone text messaging to promote healthy lifestyle and its relation in reducing in first ever CAD patients in Pakistan. Our study reported total 86 deaths (3.2%) during the course of data collection (18 months). If we exclude those participants whom we did not had any contact during subsequent follow-up, e.g., wrong numbers and constantly off, percentage only shifts from 3.2% to 4.2%. To the best of our knowledge we did not find any scientific evidence of such a low mortality rate in our study participants or in SA population in general. A possible explanation for this might be that SA suffer their first ever cardiac assault at an earlier age (compared with Western population), and young aged patients might be more capable of surviving a cardiac assault. There is a

scarcity of valid mortality data from Pakistan [97, 190, 191], and to our knowledge, our study is one of very few studies, which contribute in reporting mortality among first ever CAD patients. One study conducted in Pakistan to determine the outcome of primary percutaneous intervention (PCI) reported that mortality rate was 7.9% during their six months' study period which comprised of 5.9% dying while still in hospital and a further 2% dying after six months' follow-up [192]. One-year retrospective review of death certificates and hospital charts of patients dying on general and specialty medical services at one tertiary care hospital in Pakistan also show that mortality was lowest in cardiology (2.26%) [97]. Studies on a mortality rate in CAD patients, done on immigrants of SA in western countries have given conflicting results. The mortality rate reported in CAD patients of SA origin in Western countries ranges from 6.1% to 10%, and among native Caucasian population it ranged from 1.5% to 8% [193-197]. One study conducted in Canada to observe outcomes following percutaneous coronary intervention in SA and white patients showed that there was no significant difference in mortality within 30 days and 1 year between SA and Caucasian patients (3% versus 2.3%) [198]. One study found significantly higher 6 months' mortality rates in SA subjects than in Caucasian (Canadian) control subjects [95]. Whereas, two other studies did not report any significant difference up to 4 years after MI between SA and Caucasian subjects [195, 199]. In Canadian studies SA had similar short term mortality but a lower long-term mortality compared with non-SA subjects [193, 194]. Another study from Canada showed higher one year mortality among SA patients than non-SA patients (6.1% versus 1.5%), and there was a difference in the risk profile between SA and non-SA [200]. Recent large studies conducted in European region showed lower mortality among SA than non-SA subjects [197, 201]. One study conducted in Netherland based on nationwide registers from 1998 to 2010, for information regarding CAD/CHF hospitalization and outcome, showed 28 days' mortality was higher in SA than Dutch subjects, whereas 5 years' mortality rate was lower in SA than Dutch subjects [196].

Results of one recent study from UK based on the retrospective analysis of CAD patients between 2004 and 2009, reported 9% mortality among immigrant SA and 7.4% mortality among white indigenous sample [202].

The intervention component of our study aimed at promoting healthy lifestyle by targeting major risk factors attributable to CAD which would have indirect effect in reducing mortality among CAD patients. Almost all the patients who died in our study did so in between baseline assessment and their first follow up, so we were unable to reassess their risk factor profile. On the basis of baseline assessment of risk factors attributable to CAD in our study patients, old age at first event of CAD, unemployment, history of diabetes mellitus, history of hypertension, and major time spent sitting on week days were found to be independently associated with mortality among CAD patients. Similar risk factors were also reported to be responsible for high mortality in CAD patients of SA immigrants in western countries. For example, a study observing difference between SA and white European in five-year outcome following percutaneous coronary intervention concluded that there was no long-term difference in all-cause mortality between SA and Caucasian European patients, despite SA having symptomatic CAD at a younger age and a higher prevalence of diabetes [203]. The explanation for high short term mortality in SA immigrants than native Caucasian European population showed, that a) SA had a higher degree of disease severity, b) high prevalence of comorbidity (particularly high prevalence of diabetes and hypertension), c) and concomitant cardiovascular risk factors [196].

Strength and Limitations

The major strength of our clinical trial is its sample size. To the best of our knowledge, this study is one of the largest mobile phone text messages based intervention in CAD patients conducted in SA. The other major strength is the inclusion of the respective patient's primary care givers, not only to target primary prevention but to have bi-directional reinforcement of

health messages. Our clinical trial is first to implement mobile phone text messaging for psychological wellbeing and observing the effect of intervention on risk factors and in turn its effect on mortality rate between intervention and non-intervention groups among patients.

Our study has several limitations that should be accounted in interpreting our trial findings. Biochemical risk factors were available in a small sample of the study population, due to resource constraint and logistical difficulties. Only 21% of the caregivers, nominated by their respective patients, consented to participate in the study, whereas 79% refused to participate. We further face rather high drop-out rate at follow-up. Despite our best effort to persuade our study participants to visit our study site for follow-up, only two thirds of the participants were able to complete first follow-up (around 66 %.). Various factors influence the relatively low rate of follow-up, including relative lack of patient compliance to travel, absence of material incentives or inducement, frequent safety and security concerns. Other factors, including ethnicity, level of education may also play a role. The study may also have an element of recall bias, as subjects may have responded positively to all risk factors introduced, knowing that the study was about heart disease and risk factors [63]. The other limitation was that we only recruited the survived (non-fatal) patients of CAD, so our result could only be attributed to survived patients, not to be generalized on the whole population of CAD patients who reached to the hospital. Finally, our study's follow-up was limited to an average of six months, which turned out not long enough to collect a sufficiently large sample of deceased participants, due to a low mortality rate in our study participants. Our data only represented population of Karachi, even though Karachi being largest and economical hub of Pakistan attracts almost every ethnic group of the country but results be interpreted with caution for different ethnic groups living in their local area.

Future Directions/recommendations for future research.

One of our study investigators (JI), who supervised data collection, conducted some in person discussions with the patients of the intervention group (around 25%) to keep an update on the compliance of patients in receiving, and reading SMS messages, and adopting a healthy lifestyle. The discussion revealed some important information by the participants to consider for planning future studies. The main issues raised by the participants are as follows:

a) Participants appreciated our health message, and equally appreciated SMS service to deliver those messages. They agree that health messages did enhance their knowledge, and motivated them to adopt the positive lifestyle, however, their main issue was how to adopt in practice those positive lifestyle habits recommended by our text messages? For example, for our promotion for physical activity to adopt daily walk, the main issue raised by the participants was the safety, security and rule of law in the country, and particularly in Karachi. The neighboring war in Afghanistan had a huge impact on Pakistan, in general, and Karachi in particular. The safety and security situation in Karachi was so bad that participants informed us that they only go out of their houses when it is absolute necessity, like on job, essential grocery shopping, etc. The other issue they raised was the scarcity of parks, and jogging track within their safe neighborhood also restrain them in adopting a daily walk, as promoted by our health messages

b) Even though many participants in the intervention group reported an increase in knowledge regarding healthy food, they also reported that their behaviours did not change because they could not afford to buy the healthy food. The bad economic situation, corruption and high inflation rate in Pakistan badly affected the income capacity and buying power of the general public. Many participants informed us that they have an extended family, and they can barely able to provide three meals a day to

their families, and that too by mainly opting for low quality or unhealthy options (like unsealed saturated fat). Providing fresh fruits and vegetables regularly was beyond their means. Low buying power also had a negative impact on regular purchase of their prescribed medication.

The issues pointed out by the participants of our intervention group can be validated by the widely published report on safety and security situation [22, 164, 204, 205], economic condition (recent World Bank report show that over 50% of Pakistan's population is living below the poverty line, less than $ 1.25 a day) [206], food poverty [207], expenditure on health [149], and provisions of health facilities for general public in Pakistan [149]. The above-mentioned issues could have refrained a portion of motivated population of the society to adopt the healthy lifestyle; however, there are other, cultural and other related factors that can influence other section of the population not to adopt healthy lifestyle, especially in SA communities. Studies conducted in the western region on SA immigrants show that most SA know about positive lifestyle and healthy options but few adopt those healthy options [208, 209].

One of the probable solutions to help make text messaging as an effective intervention for the psychological wellbeing among CAD patients and their caregiver, could be to combine it with the proven beneficial preventive strategies. The combination could be initial short term face to face psychotherapy, with mid-term telephone-delivered psychological health coaching, and then sustaining it with long term positive reinforcing psychological wellbeing mobile phone text messaging, the other combination could be a short term face to face psychotherapy and then long term support with internet based health education, social media support (like, facebook, WhatsApp, Skype etc.) and supportive text messages. These combination of multiple interventions may prove to be effective, sustainable and cost effective. A recent pilot study in Germany by Van den Berg and colleague experimented with the combination of telephone

based coaching and weekly mobile phone text messages for 6 months on therapy theme[111]. The study found promising results for the combination strategy and further research was recommended for combination therapy. More and more researchers are recently concentrating their strength in the combination of interventions with mobile phone text messaging as the primary intervention [111, 214-218]. Further research on recommended strategies may benefit in promoting the psychological wellbeing of the CAD patients and their caregivers, especially in low and middle income countries.

Study conducted in Finland by Kauppi et al., to deliver health messages to patients receiving antipsychotic medication found that Monday was the most popular day to receive messages, morning was preferred to later in the day, older women and younger men preferred higher number of messages, participants preferred positive, encouraging and slightly humorous messages [219]. Based on recent published results it could be recommended that the success of future mobile phone text messages based studies most probably be dependent on intervention duration, text message frequency, level of interactivity, culturally tailored messaging, timing of messages, content, and local acceptability.

CONCLUSION

We designed a prospective, randomized controlled, single blinded clinical trial in Pakistan to study the benefits of SMS targeting major modifiable risk factors associated with CAD. A novel approach was used to address the "Caregiver Strain" by recruiting caregivers as a parallel group along with their respective CAD patients. The characteristics of the participants between and within group are comparable at baseline assessment which show that our randomization was effective and valid.

It is somewhat surprising that SMS based intervention was not effective in promoting psychological wellbeing in our study subjects. The potential explanation for the non-effectiveness of our intervention may be explained as first, the majority (more than 63% of

study subjects) scored as not being suffering from depression or anxiety, and those who had symptoms of depression or anxiety, majority of them were mildly depressed (more than 90%). This left us with little room for improvement, and text messages alone may not be convincing enough to have positive impact on their psychological wellbeing. Second, even though we can increase the length of message by increasing the character but it would increase the cost of the message as each message is cost by count of characters in a message. Third, individuals to be diagnosed as suffering from anxiety and depression even in the presence of standardized screening tools/instruments could reflect a recall bias, as one of the limitation [182]. Fourth, it has been acknowledged by previous studies that participants may be reluctant to acknowledge a formal diagnosis of anxiety or depression because of the stigma associated with mental illness [183-186]. Studies conducted in Pakistan reported that participants hide their true feelings due to social stigma, as people surrounding them have negative feeling about it [187, 188]. The above mentioned biases could also have influenced the outcome of our study too. Fifth, different geographical areas (even in one country) and culture can influence the prevalence of depression and anxiety. A study conducted in three provincial capital cities of Pakistan reported prevalence of depression in Lahore at 53.4%, in Quetta (43.9%), and in Karachi (35.7) [164]. It was surprising to note that Karachi with relatively worst safety and security situation, violence, street crimes, terrorism and lawlessness showed relatively lowest prevalence of depression, whereas in Lahore, where safety and security situation is relatively better, and had wider exposure to psychiatric services, people are more expressive and had the highest proportion of people with depression as compared to other two cities. The explanation provided by the study was, that geographical area, language, and cultural background can influence the prevalence rate of depression and anxiety in that population [164]. Cultural influence on adopting positive lifestyle by SA was reported by a recent stud, investigators found out that SA are reluctant to accept that they can prevent the CAD, and not willing to improve their

knowledge regarding major modifiable risk factors attributable to CAD [220, 221] SA tend to continue with their previous dietary habits, even after suffering a cardiac event [222]. One study also found that SA do not accept publicly to a healthy dietary or lifestyle program, possibly through fear of alienation from their community [223, 224] On dietary habits of SA researchers found that SA tend to eat significantly fewer meals per day than Caucasian, with a large late evening meal, and that pattern of dietary habit produces hypoglycemia in day and hyperglycemia in night, which also adversely affect their digestion and sleep patterns [225]. SA also overcook vegetables, which destroys their nutrient content [226]. Study conducted in in UK of SA women found that regular physical activity by women is culturally unacceptable, and considered as a cause of physical weakness [15, 227]

Psychological wellbeing is proven to be responsible for the overall health of an individual. Even though, our SMS based intervention was not effective in promoting psychological wellbeing in our intervention group of CAD patients and their caregivers, but it may provide an opportunity to rethink about implementing said intervention in a different way, and may be considering all the issues discussed earlier, for it to be effective for psychological wellbeing of the CAD patients and their caregivers. Our clinical trial also concluded that mobile phone text messages may be ineffective in reducing mortality rates over such a short follow-up period. However, the study did find that unemployment, history of diabetes and hypertension, and non-physical activity were independent risk factors for premature mortality over a 6-month follow-up. Future research should therefore particularly aim to target these modifiable risk factors in order to reduce mortality rates in CAD patients living in Pakistan.

Perseverance in educating the patients of CAD and their care-givers to change the belief that early disease and death are inevitable, and encourage them that means for improvement via adopting healthy lifestyle modification can reduce CAD burden in their community, could be the key to success.

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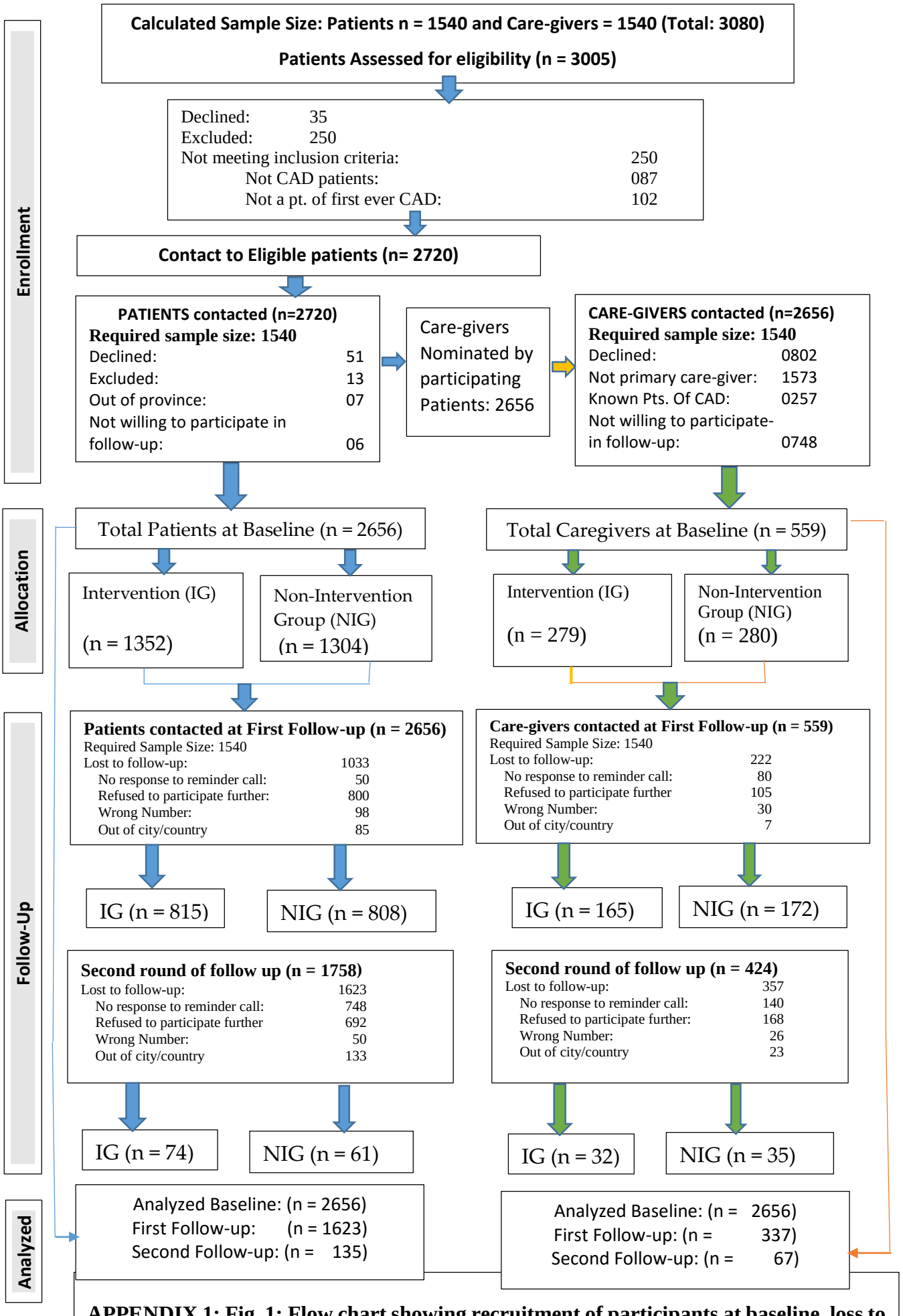
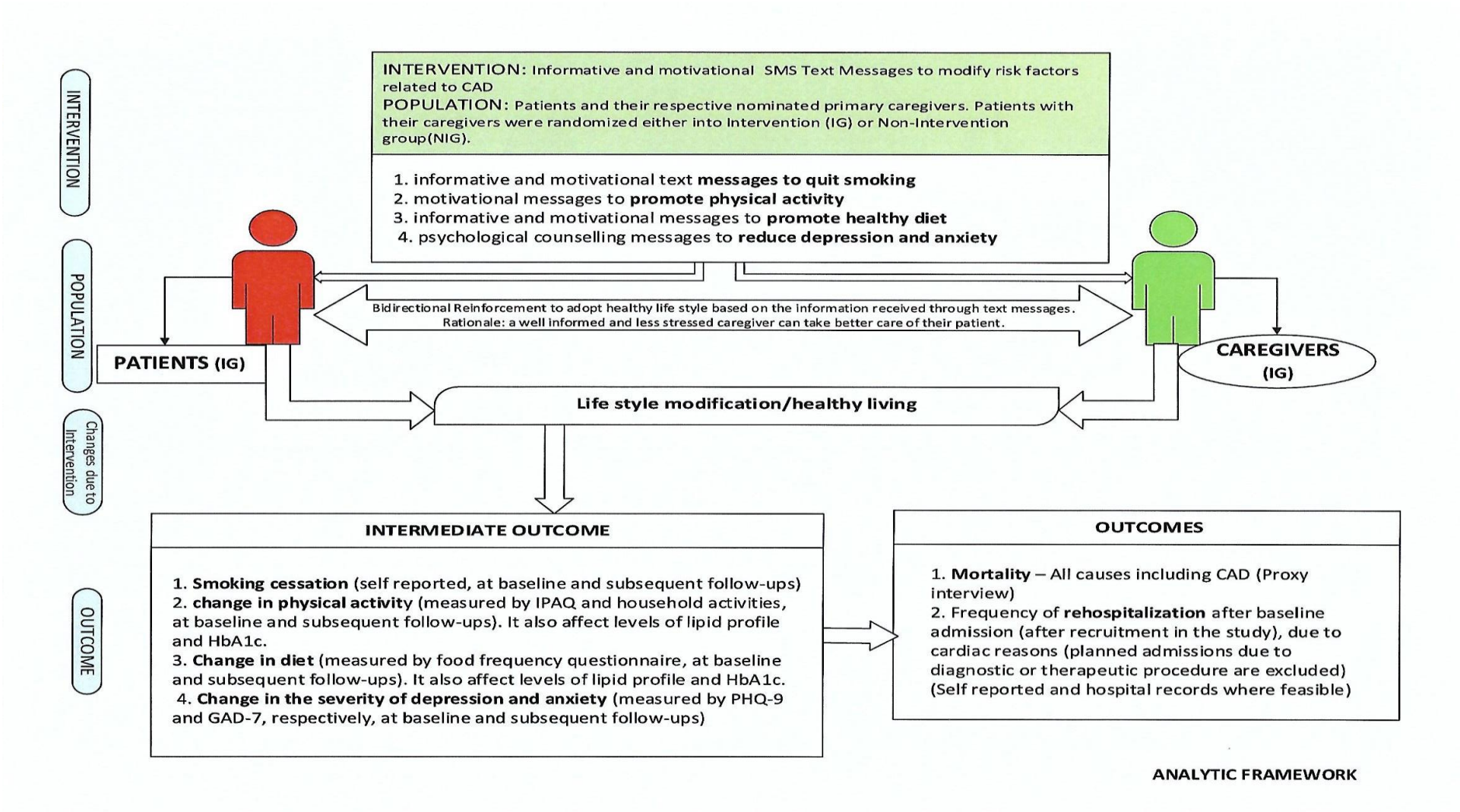
APPENDICES



APPENDIX 1: Fig. 1: Flow chart showing recruitment of participants at baseline, loss to follow-up and recruitment at each follow-up

APPENDIX 2: Fig. 2: Conceptual Diagram of the study Design



APPENDIX 3: Study Questionnaire

THE UTILITY OF MOBILE PHONE IN THE PREVENTION OF CORONARY HEART DISEASE THROUGH LIFESTYLE MODIFICATION – A RANDOMIZED CONTROLLED CLINICAL TRIAL

ANZCTR Reg. No: ACTRN12611000388910

Ethics Approval (Macquarie University) Ref. NO: 5201100109

Study Sites: ✞KIHD ✞NICVD ✞Tabba Heart -

Date:_____

Study R. No. _____ Cell. No. _____

F U D: _____ Labs. ☐ ☐ Date: _____

BASELINE DATA FORM

(Cross Each Corresponding Box e.g., **X**)

DEMOGRAPHICS: **ADMISSION:** Date: _____

Name: _____ _____ Adm. Location: ☐ Angio. ☐ Ward ☐ CCU

Gender: ☐ Male ☐ Female ☐Patient ☐Care giver

Address: _____ **DISPOSAL MODE:** Date: _____

Land line Tel # (____) _____ ☐ D/C to Home ☐ Referred ☐ Death

Cell # (_____) _____

Email:_____

DOB: ____/____/____ (dd/mm/yy) AGE: _____ (Years)

Marital Status: _____ Ethnicity: _____

Formal Education: ☐ Yes ☐ No: Level of Edu. :_____

Informal Education : ☐ Yes ☐ No: Level of Edu. :_____

Employed: ☐ Yes ☐ No ☐ Retired

If yes, Occupation ☐Private ☐Public ☐Business No. of Jobs: _____

Nature of Occupation: J1☐Desk-Job ☐Physical

J2☐Desk-Job ☐Physical

Main illness

Prim. Disease. (ICD 10)

_____

Sec. Disease. (ICD 10)

1_____

2_____

3_____

Consulting Physician:

_____

Patient's Presentation *(From File, Otherwise Ask From Patient)*

Date of cardiac Insult: _____/_____/_____
Time symp: _____ Time arrv. Hosp: _____ Time protocol : _____

Symptoms:

Chest Discomfort/Pain: ☐ Yes ☐ No- If yes, Angina☐ Yes ☐ No - If yes, ☐Stable Angina ☐USA CCS Class: ☐ I ☐ II ☐ III ☐ IV - ☐ Definite ☐ Possible

MI: ☐ Yes ☐ No : If yes, ☐ Non-ST elevation MI ☐ ST-elevation MI

Time period: ☐ <6h ☐ 6-24h ☐ 25h-7d

☐ Dizziness ☐ Sweating ☐ Fatigue ☐ Abdominal pain ☐ Shortness of Breath ☐ Headache

☐ Palpitations ☐ Nausea/Vomiting ☐ Anxiety/ Ghabrahat ☐ Claudication/Limb pain

Signs:

☐ Clubbing ☐ Raised JVP ☐ Murmur/Thrill ☐ Anuria ☐ Bluish discoloration ☐ Carotid bruit

☐ Syncope ☐ Edema ☐ Hepatic/Spleenomegaly ☐ Crepts/Rales ☐ Paroxysmal nocturnal dyspnea

☐Infective/Fever/Inflammatory Any other 1:_____ 2:_____ 3:_____ 4:_____

PRESENT VITALS: *(From Charts) Date:* _____
BP : Sys_____ Dias_____Temperature: _____◦C/◦F Pulse : _____ /min RR: _____ /min

Risk Factors: *(Ask From patient/consult medical record)*	
A1	Family history of premature CAD (≤ 50 years), ☐ Yes ☐ No **If Yes:** Relationship_____
A2	Were the subject's Father and Mother were first degree relatives? ☐ Yes ☐ No
A3	**Dyslipidemia** (diagnosed / treated by physician) ☐ Yes ☐ No, If Yes, Therapy:☐Statins ☐Non-Statin
A4	**Diabetes** ☐ Yes ☐ No If Yes, since _____(wk/mth/yrs), Therapy: ☐Diet ☐Oral ☐Insulin
A5	**Hypertension** ☐ Yes ☐ No, since _____ (wk/mth/yrs)

A6(In fat least for the last 6 mnths	**Smoking Tobacco**, ☐ Yes ☐ No If No: Ever Smoked ☐ Yes ☐ No, If Yes go to QA7 Status: ☐ Current Since _____ (wk/mth/yrs), Type: ☐Cigarette, # _____ (day/wk/mth), ☐Hukka, Quantity _____ (day/wk/mth) ☐Sheesha, Quantity _____ (day/wk/mth)
A7	☐ Former/Ex-smoker (If quit > 6 months, more than 2 years) how Long _____ (wk/mth/yrs), Type: ☐Cigarette, # _____ (day/wk/mth), ☐Hukka, Quantity _____ (day/wk/mth) ☐Sheesha, Quantity _____ (day/wk/mth)
A8(In fat least for the last 6 mnths	Smokeless Tobacco ☐ Yes ☐ No, If Yes, Type: ☐ Naswar, _____(day/week/month) ☐ Chewing Tobacco, _____(day/week/month) ☐ Gutka/main puri, _____(day/week/month)
A9	Chronic lung disease: ☐ Yes ☐ No If Yes, Specify_____
A10	Contraceptive pills *(females only)* ☐ Yes ☐ No
A11	Alcoholism: ☐ Yes ☐ No frequency: Daily/Weekly/Monthly, Amount _____
A12	Illicit (Marijuana/Cocaine/Opium/Heroin) drug use☐ Yes ☐ No, Amount: _____
A13	Any Other: 1._____ 2._____ 3. _____ 4._____
A14	Any Comment:

Physical / Labs: (Baseline)

Date	Test	Result	Date	Test	Result
	O_2 Sat.	%		Creatinine	mmol/L
	Cholesterol	mg/dL		TLC	/mm3
	Triglycerides	mg/dL		HbA1C	%
	Hb	g/dL		LDL	mg/dL
	Serum Ca+:			HDL	mg/dL
	Serum K+:			Urea	mmol/L
	RBS/FBS	mg/dL		CRP	mg/L
	Homocysteine	µg/L		Trop I	µmol/L
	Protein. C/S def	☐ Yes ☐No		High factor VII	☐ Yes ☐No
	High fibrinogen	☐ Yes ☐No			

Killip Class ☐ I ☐ II ☐ III ☐ IV Weight: _____ Kgs Height: _____cm

Abd. Girth: _____cm Hip circ.:_____cm

ECG Findings: *(From File, Otherwise Ask From Physician)*	
Rate	_____ /min ☐Tall R in V1-V2
Rhythm	☐Sinus ☐Atrial Fibrillation / Flutter ☐Paced ☐SVT ☐VT ☐Others
Q waves	☐Baseline Q Waves ☐New Q-Waves on FUP ECG
Conduction	☐Presumed New LBBB ☐Old LBBB ☐RBBB ☐RBBB with left hemi-blocks
Heart blocks	☐First degree ☐Second degree type I ☐Mobitz type –II/third degree AV-block.
ST- Elevations	☐Inferior II, III, AVF ☐Anterior V1-V4 ☐Lateral V5-V6, I, AVL
ST-Depression	☐Inferior II, III, AVF ☐Anterior V1-V4 ☐Lateral V5-V6, I, AVL
T-Wave inversion	☐Inferior II, III, AVF ☐Anterior V1-V4 ☐Lateral V5-V6, I, AVL
Tall T-Waves	☐Inferior II, III, AVF ☐Anterior V1-V4 ☐Lateral V5-V6, I, AVL

Medications at Discharge: *(From File, Otherwise Ask From Physician)*			
Drug	**Dosage**	**Drug**	**Dosage**
☐ Aspirin		☐ Diuretics	
☐ Antiplatelet		☐ Nitrates	
☐ Antithrombotic		☐ Digoxin	
☐ Vasopressors		☐ Warfarin	
☐ Lipid lowering		☐ Class I (AA)	
☐ Beta-Blockers		☐ Class III (AA)	
☐ ACE-I		☐ Vasodilators	
☐ ARB		☐ Insulin	
☐ Ca-Antagonists		☐ Diuretics	
		☐ Oral anti-diabetic	

Recent Thrombolytic Therapy: *(From File, Otherwise ask from Patient)*	
	Thrombolytic therapy given? ☐ Yes ☐No ☐UK If Yes, Date:___/___/___
	Type of thrombolytic agent given☐ SK ☐tPA ☐Other

Complic-ations	☐IntC. Hemorrhage ☐Sys. Hemorrhage ☐Groin Hematoma ☐None ☐Not applicable ☐Others:_____
	Contraindication to thrombolytic therapy☐ Yes ☐No, If yes, Specify _____

Hospital Course / Evaluation: *(See From File)*

(Nd=Not done, P=Positive, N=Negative, E=Equivocal, A=Arrhythmia, TTE=Transthoracic Echocardiography, TEE= Transesophageal Echocardiography)

☐Required Hemodynamic support ☐ Yes ☐No

☐Invasive Monitoring: ☐IABP ☐Arterial line ☐CP Bypass ☐CVP ☐Swan-Ganz

Echocardiographic Findings

☐LV Wall motion ☐Normal ☐Abnormal

☐Echocardiogram ☐TTE ☐TEE

Chambers Enlarged: ☐LA ☐LV ☐RA ☐RV

LVDD ☐Yes ☐No: Grade ☐I ☐II ☐III LV clot ☐Yes ☐No LVH ☐Yes ☐No

☐Ejection Fraction checked**; _____%** ☐Estimated ☐Calculated ☐Contrast ☐Echo ☐Radionuclide

Patient Plan At Discharge *(See From File)*

LABS: ☐ CBC ☐UCE ☐Lipid Profile ☐Blood Sugar Fasting ☐Blood Sugar Random

Labs done by the Study : ☐Lipid Profile ☐HbA1c Date: _____

Cardiac specific evaluation/investigations:

☐ECG ☐Angiography ☐Echo ☐Radionuclide Scan

☐Other 1_____,
2_____,3_____

ANGIOGRAPHY - ANGIOPLASTY

ID:		**Name:**		**Date**	

S.N	Date	Cath #	Location:	Procedure nature:	Diagnosis
1.			☐ KIHD ☐ Outside	☐ Diagnostic ☐	
2.			☐ KIHD ☐ Outside	☐ Diagnostic ☐	
3.			☐ KIHD ☐ Outside	☐ Diagnostic ☐	

RECENT CATHETERIZATION AT KIHD:	**Date**		**Cath #**	
Statu	☐ Elective ☐ Urgent ☐ Emergency ☐	**Catheter size**	☐ 5-F ☐ 6-F ☐ 7-F	
Indications	☐ MI ☐ Stable angina ☐ USA ☐ Positive exercise stress test ☐ Chronic total occlusion			

Catheter	☐ Radial ☐ Femoral ☐ Brachial						
ANGIOGRAPHIC INFORMATION:		**EF**	**%**	**Duration**			
LM	**%. Other abnormalities**			**Dominance**	☐ Right ☐ Left ☐ Co-dominant		
LAD	**Osteal**	**Prox**	**Mid**	**Distal**	**D1**	**D2**	**S1**
	%	%	%	%	%	%	%
LCX	**Osteal**	**Prox**	**Mid**	**OM1**	**OM2**	**OM3**	**Distal**	**LPDA**	**Ramus**
	%	%	%	%	%	%	%	%	%
RCA	**Osteal**	**Prox**	**Mid**	**Distal**	**RPDA**	**RPLV**	**AcuteM**
	%	%	%	%	%	%	%
Segmental LV function:				**Diagnosis:**	☐ No vessel ☐ SVD ☐ 2VD ☐ 3VD		
Recommendation:	☐ Medical treatment ☐ PCI _____ ☐ CABG ☐ Early CABG						
CABG INFORMATION:	☐ Yes ☐ No ☐ Not done			**CABG Date:**			

Vessel	**Site**	**Conduit**	**% Stenosis**	**Others**	**Site**	**Conduit**	**% Stenosis**	**Others**
RCA								
LCX								
LAD								

ANGIOPLASTIC INFORMATION:	**Date**		**Cath #**		**Size**	☐ 5-F ☐ 6-F ☐ 7-F	
Status	☐ Elective ☐ Urgent ☐ Emergency ☐ Salvage			**Access:**	☐ Radial ☐ Femoral ☐ Brachial		

No	**Vessel**	**Site**	**Lesion**	**Balloon**	**Stent**	**BMS**	**DES**	**PostBalloon**	**Outcome**
1.				☐ Yes ☐ No	☐ Yes ☐ No			☐ Yes ☐ No	☐ S ☐ P ☐ F
2.				☐ Yes ☐ No	☐ Yes ☐ No			☐ Yes ☐ No	☐ S ☐ P ☐ F
3.				☐ Yes ☐ No	☐ Yes ☐ No			☐ Yes ☐ No	☐ S ☐ P ☐ F
4.				☐ Yes ☐ No	☐ Yes ☐ No			☐ Yes ☐ No	☐ S ☐ P ☐ F

No	**Balloon**	**Balloon dia**	**BMS name**	**BMS dia**	**DES name**	**DES dia**
1.						
2.						
3.						
4.						

PRESSURE	AORTA (mm Hg)			L.V. (mm Hg)		PRESSURE	AORTA (mm Hg)			L.V. (mm Hg)	
	S	D	M	S	EDP		S	D	M	S	EDP
PRE-ANGIO						*POST-ANGIO*					

Procedure Outcome		
☐ Successful	☐ Partial	☐ Unsuccessful

Intra-Procedure Complications	
☐ Anaphylaxis/ Allergic Reactions	☐ Pyrogen Reaction
☐ Nausea/Vomiting	☐Catheter induced Vasospasm
☐ Metallic taste, Burning in throat	☐ Slow reflow
☐ No reflow/Complete stenosis	☐Stent dislodgement/displacement
☐ Dissection at site of Balloon Expansion	☐ Arrythmia
☐ Perforation at site of balloon Expansion	☐ Hypotension
☐ Macroscopic embolization	☐ Volume Overload
☐ Other 1 _____	☐ Other 2 _____ ☐ Other 3_____

Vascular Access-Site Problems		
☐ Bleeding	☐ Hematoma	☐ Vessel Dissection
☐ Occlusion	☐ Femoral Nerve Injury	

Post Procedure Complaints/Findings/Complications
Specify if any:

Vascular access-site problems
☐Bleeding ☐Hematoma ☐Pseudo-hematoma ☐Occlusion ☐Fistula ☐Loss of Distal pulse ☐Wound discharge

PATIENT PLAN AT DISCHARGE

LABS
☐ CBC ☐UCE ☐Lipid Profile ☐Blood Sugar Fasting ☐Blood Sugar Random ☐Other 1_____, 2_____,3_____

ROSE QUESTIONNAIRE

A. CHEST PAIN ON EFFORT

A1. Have you ever had any pain or discomfort in your chest?

☐ Yes ☐ No

If "no' proceed to Section C.

A2. Do you get this pain or discomfort when you walk uphill or hurry?

□ Yes □ No □ Never hurries or walks uphill

If "No", proceed to Section B.

A3. Do you get pain or discomfort when you walk at an ordinary pace on the level?

□ Yes □ No

A4. What do you do when you get pain or discomfort while you are walking?

□ Stop or slow down □ Carry on

If "Carry on", proceed to Section B.

(Record "stop or slow down" if subject carries on after taking sublingual tablet nitroglycerine)

A5. When you stand still, what happens to pain or discomfort?

□ Relieved □ Not relieved

If "Not relieved", proceed to Section B.

A6. How soon, does this pain or discomfort go away?

□ ≤ 10 minutes □ > 10 minutes

If "> 10 minutes", proceed to Section B.

A7. Will you show me where pain or discomfort was? (FIGURE)

(More than one response possible) □ Sternum (upper or middle) □ Sternum (lower)

□ Left anterior chest □ Left arm

□ Other, specify

_____

A8. Did you feel pain or discomfort anywhere else?

□ Yes □ No

A9. If yes specify:

_____

B. <u>POSSIBLE INFARCTION:</u>

B1. Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

□ Yes □ No

C. <u>INTERMITTENT CLAUDICATION</u>

C1. Do you get pain in either leg on walking?

□ Yes □ No

If "No", proceed to Section D.

C2. Does this pain ever begin when you are standing still or sitting?

□ Yes □ No

If "Yes", proceed to Section D.

C3. In what part of your leg do you feel it?

□ Pain includes calf/ calves
□ Pain does not include calf/ calves

If calves not mentioned, ask anywhere else (specify)

_____

If "Pain does not include calf/ calves", proceed to Section D.

C4. Do you get it when you walk uphill or hurry?

□ Yes □ No □ Never hurries or walks uphill

If "No", proceed to Section D.

C5. Do you get it when you walk an ordinary pace on the level?

□ Yes □ No

C6. Does the pain ever disappear while you are walking?

□ Yes □ No

If "Yes", proceed to Section D.

C7. What do you do if you get it when you are walking?

□ Stop or slow down □ Carry on

If "Carry on", proceed to Section D.

C8. What happens to it if you stand still?

□ Relieved □ Not relieved

If "Not relieved", proceed to Section D.

C9. How soon?

□ ≤ 10 minutes □ > 10 minutes

D. INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

Short Last 7 Days Telephone IPAQ

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities?

_____ Days per week [VDAY; Range 0-7, 8,9]

8. Don't Know/Not Sure
9. Refused

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

__ __ Hours per day [VDHRS; Range: 0-16]

__ __ __ Minutes per day [VDMIN; Range: 0-960, 998, 999]

998. Don't Know/Not Sure
999. Refused
__ __ Hours per week [VWHRS; Range: 0-112]
__ __ __ __Minutes per week [VWMIN; Range: 0-6720, 9998, 9999]
9998. Don't Know/Not Sure
9999. Refused

3. During the **last 7 days**, on how many days did you do **moderate** physical activities?

____ Days per week [MDAY; Range: 0-7, 8, 9]

8. Don't Know/Not Sure
9. Refused

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

__ __ Hours per day [MDHRS; Range: 0-16]
__ __ __ Minutes per day [MDMIN; Range: 0-960, 998, 999]

998. Don't Know/Not Sure
999. Refused
__ __ __ Hours per week [MWHRS; Range: 0-112]
__ __ __ __Minutes per week [MWMIN; Range: 0-6720, 9998, 9999]
9998. Don't Know/Not Sure
9999. Refused

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

____ Days per week [WDAY; Range: 0-7, 8, 9]

8. Don't Know/Not Sure
9. Refused

6. How much time did you usually spend **walking** on one of those days?

__ __ Hours per day [WDHRS; Range: 0-16]
__ __ __ Minutes per day [WDMIN; Range: 0-960, 998, 999]

998. Don't Know/Not Sure
999. Refused
__ __ __ Hours per week [WWHRS; Range: 0-112]

__ __ __ __Minutes per week [WWMIN; Range: 0-6720, 9998, 9999]
9998. Don't Know/Not Sure
9999. Refused

7. During the last 7 days, how much time did you usually spend ***sitting*** on a **week day**?

__ __ Hours per weekday [SDHRS; 0-16]

__ __ __ Minutes per weekday [SDMIN; Range: 0-960, 998, 999]

998. Don't Know/Not Sure
999. Refused

__ __ Hours on Wednesday [SWHRS; Range 0-16]

__ __ __ Minutes on Wednesday [SWMIN; Range: 0-960, 998, 999]

998. Don't Know/Not Sure
999. Refused

TO BE COMPLETED BY PARTICIPANT	*TO BE COMPLETED BY INTERVIEWER*
Did you perform this household activity in the past 12 months?	
1a. Climbing up stairs at home? *NO* 2 ☐ *YES* 1 ☐ (30)	1b. How many months did you climb up stairs? ☐☐ (31) *MONTHS* 1c. How many times per day did you climb up stairs? ☐☐☐ (33) *TIMES* 1d. Between how many floors did you walk up each time? ☐☐ (36) *FLOORS*
2a. Major cleaning (garage, car, rugs, scrubbing floors) *NO* 2 ☐ *YES* 1 ☐ (38)	2b. How many months did you do major cleaning? ☐☐ (39) *MONTHS* 2c. How many times per month did you do major cleaning? ☐☐☐ (41) *TIMES*
3a. Light cleaning (dusting, vacuuming, straightening up, changing linen) *NO* 2 ☐ *YES* 1 ☐ (44)	3b. How many months did you do light cleaning? ☐☐ (45) *MONTHS* 3c. How many times per month did you do light cleaning? ☐☐☐ (47) *TIMES*
4a. Grocery shopping *NO* 2 ☐ *YES* 1 ☐ (50)	4b. How many months did you grocery shop? ☐☐ (51) *MONTHS* 4c. How many times per month did you grocery shop? ☐☐☐ (53) *TIMES*
5a. Other shopping *NO* 2 ☐ *YES* 1 ☐ (56)	5b. How many months did you do other shopping? ☐☐ (57) *MONTHS* 5c. How many times per month did you do other shopping? ☐☐☐ (59) *TIMES*
6a. Making beds *NO* 2 ☐ *YES* 1 ☐ (62)	6b. How many months did you make beds? ☐☐ (63) *MONTHS* 6c. How many days per week did you make a bed? ☐ (65) *DAYS* 6d. How many beds per day did you make? ☐☐ (66) *BEDS*
7a. Doing laundry *NO* 2 ☐ *YES* 1 ☐ (68)	7b. How many months did you do laundry? ☐☐ (69) *MONTHS* 7c. How many loads of laundry per week did you do? ☐☐ (71) *TIMES*

TO BE COMPLETED BY PARTICIPANT		TO BE COMPLETED BY INTERVIEWER	
Did you perform this household activity in the past 12 months?			
8a. Preparing meals, doing baking projects	NO 2 ☐ YES 1 ☐ (73)	8b. How many months did you prepare meals or do baking projects?	☐☐ MONTHS (74)
		8c. How many times per week did you prepare quick meals?	☐☐ TIMES (76)
		8d. How many times per week did you prepare elaborate meals or do baking projects?	☐☐ TIMES (78)
9a. Washing dishes	NO 2 ☐ YES 1 ☐ (80)	9b. How many months did you wash dishes?	☐☐ MONTHS (81)
		9c. How many times per week did you wash dishes?	☐☐ TIMES (83)
10a. Another activity specify: _____	NO 2 ☐ YES 1 ☐ (85)	10b. How many months did you do this?	☐☐ MONTHS (86)
		11c. How many times per month did you do this?	☐☐☐ TIMES (88)
11a. Another activity specify: _____	NO 2 ☐ YES 1 ☐ (91)	11b. How many months did you do this?	☐☐ MONTHS (92)
		11c. How many times per month did you do this?	☐☐☐ TIMES (94)

E. DIET ASSESSMENT QUESTIONNAIRE

I would like you to tell me how often you eat these foods in a day/week/ month.

FOOD Items	Never	- /month	/ week	/ day
Eggs.				
Eggs White only				
"Paratha"				
Tandoori Naan				
"Halwah Puri"				

Milk whole (with cream or balai)				
Milk without cream or balai (Skimmed)				
Cream or malai/Balai.				
Milk Dessert e.g. custard, kheer, firni etc.				
Ice cream.				
Dahi (malai - without malai)				
Lassi sweet (malai - without malai - Sweet / Salt)				
Kata kat, Karahi, Nehari,				
Margarine / Butter				
Mutton (Salan, roasts, etc.).				
Beef (salan, roasts, kabab, qeema etc.).				
Chicken (salan, roasts, tikka etc.).				
Fish (salan, fry, etc.).				
Prawns, other shell fish (lobsters, crabs etc.).				
Organ Meats (Liver, brain - etc.).				
Eat foods such as. burgers , Pizza, etc.).				
Cooked Vegetables (not including potatoes).				
Potatoes (including other vegetables and meat).				
Uncooked Vegetables (raw e.g. in salad).				
(Biryani/plaoo).				
Beans lentils, peas, dal.				
Fruits, not counting juices.				
Fresh Fruit juices, not including packaged drinks like frost etc.				
Soft drinks (Regular - Diet)				
Bakery products (e.g. cakes, pastries, Biscuits etc.).				
Mithais, Halwas.				
Salty/fried snacks, such as potato chips, popcorn, samos, pakorah kababs, nimco etc.				
Nuts: e.g. peanuts, almonds, chilgoza.				

Chocolate and other candies.				
Plain rice				
Salad (with cream – without cream)				
Any other food that you consume regularly and we have not asked about it?				
a) Multi Vitamins -				
b)				
c)				

►Do you put extra salt on Food □ Yes □ No ►How Often

_____

►Do you put salt on Salad □ Yes □ No

►What kinds of fat do you usually use in cooking (e.g. cooking salan, frying etc.)?

_____

►What brand of Ghee/Oil do you use? Asli Ghee _____ Ghee _____ Oil

_____

Office use only		PHQ-9		GAD-7		Global	

نام | تاریخ

گزشتہ 2 ہفتوں کے دوران، آپ کو درج ذیل مسائل کی وجہ سے کتنی مرتبہ مشکل پیش آئی ہے؟

PHQ-9	خانے میں اپنے جواب کی نشاندہی کرنے کے لئے " ✓ " استعمال کیجئے	بالکل نہیں	کئی دن	آدھے دن سے زیادہ	تقریباً روزانہ
1	کچھ بھی کرنے میں بہت کم دلچسپی یا خوشی ہوتی ہے۔	0	1	2	3
2	پژمردہ، افسردہ یا ناامید ہونا۔	0	1	2	3
3	سونے یا سوئے رہنے میں مشکل ہونا، یا بہت زیادہ سونا۔	0	1	2	3
4	تھکان محسوس کرنا یا بہت کم توانائی محسوس کرنا۔	0	1	2	3
5	بھوک میں کمی یا بہت زیادہ کھانا۔	0	1	2	3
6	اپنے متعلق برا محسوس کرنا ۔ یا یہ کہ آپ ناکارہ ہیں یا آپ نے خود کو یا اپنے خاندان کو مایوس کیا ہے۔	0	1	2	3
7	کسی کام میں توجہ مرکوز کرنے میں مشکل ہونا، جیسے کہ اخبار پڑھنا یا ٹی وی دیکھنا۔	0	1	2	3
8	اتنا آہستہ حرکت یا بات کرنا جسے دوسرے لوگ محسوس کر سکتے تھے؟ یا اس کا الٹ ۔ اتنی بے چینی محسوس کرنا کہ آپ معمول سے زیادہ حرکت کریں۔	0	1	2	3
9	اس قسم کے خیالات آنا کہ آپ کا مر جانا ہی بہتر ہے یا خود کو کسی طریقے سے تکلیف پہنچانے کے بارے میں سوچنا۔	0	1	2	3

GAD-7	خانے میں اپنے جواب کی نشاندہی کرنے کے لئے " ✓ " استعمال کیجئے	بالکل نہیں	کئی دن	آدھے دن سے زیادہ	تقریباً روزانہ
1	حواس باختہ، مضطرب یا بے بس محسوس کرنا	0	1	2	3
2	فکر کرنا بند نہ کرنا یا اس پر قابو نہ پانا۔	0	1	2	3
3	مختلف چیزوں کے بارے میں بہت زیادہ فکر کرنا۔	0	1	2	3
4	سستانے میں مشکل محسوس کرنا۔	0	1	2	3
5	اتنا بے چین محسوس کرنا کہ ایک جگہ بیٹھنا مشکل ہو۔	0	1	2	3
6	بہت آسانی سے ناراض یا غصہ ہو جانا۔	0	1	2	3
7	یہ ڈر محسوس کرنا کہ کچھ برا ہونے والا ہے	0	1	2	3

اگر آپ نے مذکورہ بالا مسائل پر نشان لگائے ہیں تو ان مسائل نے آپ کے کام کرنے، گھر میں صورتِ حال سے نمٹنے، یا دوسرے لوگوں کے ساتھ تعلقات رکھنے کو کتنا مشکل بنایا ہے؟

☐ بالکل مشکل نہیں بنایا ہے ☐ کچھ حد تک مشکل بنایا ہے ☐ بہت مشکل بنایا ہے ☐ حد سے زیادہ مشکل بنا ہے

APPENDIX 4: CONSENT FORM

Hosen Kiat
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Australian School of Advanced Medicine
2 Technology Place
Macquarie University NSW 2109
AUSTRALIA
Phone +612-9858-9888
hosen.kiat@mq.edu.au

RESEARCH PROJECT: THE UTILITY OF MOBILE PHONE IN THE PREVENTION OF CARDIOVASCULAR EVENTS, THROUGH LIFESTYLE MODIFICATION - A PROSPECTIVE, RANDOMIZED, CONTROLLED CLINICAL TRIAL

Information Sheet

We are conducting a study looking at the effectiveness of mobile phone as a medium to deliver positive life style messages through SMS/MMS or voice mail, in patients having their first heart attack or diagnosed as patient of Acute Coronary Syndrome, and one of their nominated primary care giver. It is known that cardiac rehabilitation and positive behavioural changes, like adopting healthy diet, engaging in physical activity, quitting smoking, taking good control of blood pressure, diabetes, etc., reduces cardiovascular events and its complications, especially if adopted by the patients in the early part of their recovery. It is known that adopting positive life style since early in life proved to be beneficial in either delaying or reducing cardiovascular events in later life. Since, there are meagre facilities available in Pakistan for cardiac rehabilitation, and health education delivery in general population, mainly due to low resources, researchers are looking for effective and cheaper source of delivery of these health education. Mobile phone is one of those technologies which are cheaper and widely available and adopted in Pakistan. We hope to prove the effectiveness of mobile phone in delivery of positive behavioural changes in cardiac patients and their primary care givers.

As you have had a heart disease diagnosed, you are eligible to participate in this research if you so choose. If you choose to participate you will be randomized to either join the group who will receive the health education through mobile phone (intervention group), or the other group who will not receive the health education through mobile phone (non-intervention group), but will be monitored and evaluated like the other group. You have equal chance of joining either group, as the randomization (placement in groups) process is blinded. With your permission, we would administer a questionnaire, asking about your socio-demographics, past medical history, physical activity, and dietary habits. Your height, weight, hip circumference, waist circumference, heart rate and blood pressure will be measured. We would also request you to donate 10 ml. of blood for the laboratory investigations of your lipid profile, HbA1c or blood sugar, and urine for the urinary analysis of urea, and creatanine. You do not have to pay for all the tests that would be done for this study, and the results will be conveyed to you as your preferred mode of delivery. We will request you to nominate one primary care giver to be included in this study, and after having his/her consent he/she will be recruited in the study, and same questionnaire and blood tests will be done. We will request you to please, attend the follow up clinics after every 3 months, for which we will send you the reminders. At each follow ups we will repeat the same procedure of administering questionnaire, anthropometric measurements, and same laboratory investigations. Those information and laboratory investigations will help us to monitor your progress, and if you are in the intervention group, will help us to tailor the health messages. If it would be convenient for you, we will request you to please update us about your health status, physical activity, dietary habits, blood pressure, etc., in between the follow ups, and as frequent as you conveniently can, through SMS or e-mail of the study centre.

MACQUARIE UNIVERSITY

Hosen Kiat
Professor of Cardiology and Medicine
Head, Cardiology and Medicine
Australian School of Advanced Medicine
2 Technology Place
Macquarie University NSW 2109
AUSTRALIA
Phone +612-9858-9888
hosen.kiat@mq.edu.au

The research is being carried out by Dr. Javed Ismail (+92 333 2110864 (Pak.), +61 340 166927 (Aus.) javed.ismail@students.mq.edu.au) under the supervision of Professor Hosen Kiat (+61 2 9858 9888 hosen.kiat@mq.edu.au) at Australian School of Advanced Medicine, Macquarie University, Sydney Australia. Study centre (phone ----- e-mail ------@----------). This research will form part of a thesis to be submitted for a PhD.

It will not in any way alter your treatment or your relationship with the doctors, if you decide not to participate in this research you are free to withdraw from the research at any time without consequence.

I agree to participate in the above study and understand that the extent of my involvement is to provide information to fill out the questionnaire, nominate one primary care giver (if patient), donate blood, and attend the follow up clinics after every three months, and that I may or may not benefit from this research.

Participant's Name:_____
(Block letters)

Participant's Signature: _____ Date:_____

Investigator's Name:_____
(Block letters)

Investigator's Signature:_____ Date:_____

Witness Name:_____
(Block letters)

Witness Signature:_____ Date:_____

The ethical aspects of this study have been approved by the Macquarie University Human Research Ethics Committee. If you have any complaints or reservations about any ethical aspect of your participation in this research, you may contact the Committee through the Director, Research Ethics (telephone (02) 9850 7854; email ethics@mq.edu.au). Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

APPENDIX 5: Ethics permission from Macquarie University

MACQUARIE University

JAVED ISMAIL <javed.ismail@students.mq.edu.au>

Final Approval- Ethics application reference-5201100109

Ethics Secretariat <ethics.secretariat@mq.edu.au> Fri, Apr 15, 2011 at 2:33 PM
To: Dr Hosen Kiat <hosen.kiat@mq.edu.au>
Cc: Mr Javed Ismail <javed.ismail@students.mq.edu.au>

Dear Dr Kiat

Re: "The utility of mobile phone in the prevention of Coronary Heart Disease, through lifestyle modification- a prospective, randomized, placebo controlled health intervention study" (Ethics Ref: 5201100109)

Thank you for your recent correspondence. Your response has addressed the issues raised by the Human Research Ethics Committee and you may now commence your research.

The following personnel are authorised to conduct this research:

Dr Hosen Kiat- Chief Investigator/Supervisor
Mr Javed Ismail- Co-Investigator

NB. STUDENTS: IT IS YOUR RESPONSIBILITY TO KEEP A COPY OF THIS APPROVAL EMAIL TO SUBMIT WITH YOUR THESIS.

Please note the following standard requirements of approval:

1. The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Human Research (2007).

2. Approval will be for a period of five (5) years subject to the provision of annual reports. Your first progress report is due on 15 April 2012.

If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. If the project has been discontinued or not commenced for any reason, you are also required to submit a Final Report for the project.

Progress reports and Final Reports are available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

4. All amendments to the project must be reviewed and approved by the Committee before implementation. Please complete and submit a Request for Amendment Form available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

5. Please notify the Committee immediately in the event of any adverse

effects on participants or of any unforeseen events that affect the continued ethical acceptability of the project.

6. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University. This information is available at the following websites:

http://www.mq.edu.au/policy/

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide the Macquarie University's Research Grants Management Assistant with a copy of this email as soon as possible. Internal and External funding agencies will not be informed that you have final approval for your project and funds will not be released until the Research Grants Management Assistant has received a copy of this email.

If you need to provide a hard copy letter of Final Approval to an external organisation as evidence that you have Final Approval, please do not hesitate to contact the Ethics Secretariat at the address below.

Please retain a copy of this email as this is your official notification of final ethics approval.

Yours sincerely
Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee

APPENDIX 6: Permission from study site: Karachi Institute of Heart Diseases

KARACHI INSTITUTE OF HEART DISEASES
ST-15, Block-16, Federal B. Area, Karachi-75950, Pakistan.
Fax No: 9246422, U.A.N. 111-123-749, Website: www.kihd.org

Dated: 2 April 2012

Dr. Javed Ismail
PhD Student
Macquarie University Sydney, NSW
Australia,

Subject: Karachi Institute of Heart Diseases as participating site for Dr. Javed Ismail PhD project.

Dear Dr Javed,

I, Prof Mohammad Ishaq, as an Executive Director of Karachi Institute of Heart Diseases, have reviewed your PhD protocol (utility of mobile phone to prevent cardiovascular diseases through life style modification - a randomized controlled clinical trial) and would like to accept your invitation into the trial on behalf of Karachi Institute of Heart Diseases.

We agree to be a participating site for the duration of the project and would be happy to extend all help to you in this project.

Thank you

Prof Mohammad Ishaq
Executive Director,
K.I.H.D

APPENDIX 7: Ethics Review Committee Approval to conduct study at Karachi Institute of Heart Diseases

Ethical Review Committee
Karachi Medical & Dental College
Phone #: 021-99260300-3
Fax #: 021-99260306

Ref No: CHS/125/12 KMDC. Date:October1,2012

Dr Javed Ismail
Assistant Professor
Department of Medical Research & CME
Karachi Institute of Heart Diseases

Sub: **Research proposal entitled "The utility of mobiles phone in the prevention of coronary heart disease through lifestyle modification-a randomized controlled Clinical Trial"**

Dear Dr. Ismail,

Referring to your research proposal mentioned above submitted for ethical review, the committee reviewed the proposal and approved it accordingly. You are directed to send an interim report of the study to the research office KMDC.

Kind Regards,

Prof. Farah Asad Mansuri
Secretary,
Ethical Review Committee
KMDC

KARACHI INSTITUTE OF HEART DISEASES

APPENDIX 8: Ethics Review Board permissions from study sites: National Institute of Cardiovascular diseases, Karachi Pakistan

NICVD

NATIONAL INSTITUTE OF CARDIOVASCULAR DISEASES
RAFIQUI (H.J.) SHAHEED ROAD, KARACHI-75510, PAKISTAN
PHONE: 99201271-10 Lines

August 17, 2012

Dr. Javed Ismail,
Assistant Professor Research & CME,
Department of Medical Research,
Karachi Institute of Heart Diseases,
Karachi.

SUBJECT: **"The utility of mobile phone in the prevention of coronary heart diseases through lifestyle modification; A randomized controlled clinical trial".**

Dear Dr. Javed,

Your application to conduct the above study at NICVD has been reviewed by the hospital. It can proceed as per protocol. The duration of the study will be one year from August 17, 2012 to February 16, 2014.

PROF. KHAN SHAH ZAMAN,
MBBS (DOW), MRCP (UK), FRCP (LON), MRCS (ENG) FCPS,
Executive Director
Professor of Cardiology & Chairman Academic Faculty
National Institute of Cardiovascular Diseases, Karachi

National Institute of Cardiovascular Diseases

APPENDIX 9: Ethics Review Board permissions from study sites: Tabba Heart Institute, Karachi Pakistan

Tabba Heart Institute
A state-of-the-art Cardiac Hospital
WHERE YOU MEET CARING, FRIENDLY PEOPLE

02.November' 2012

Dr. Javed Ismail,

Assistant professor Research and CME,

Karachi Institute of Heart Disease,

Subject: Approval for Ph.D research study at Tabba Heart Institute about **"The utility of mobile phone in the prevention of coronary heart disease through life style modification".**

Dear Dr. Javed Ismail,

This is in response of your request received for the approval of above mentioned.

The proposal has been discussed in the committee, your response adequately answers all the recommendations made by committee. The approval has been granted appropriately for the period of one year, with consensus of all members. Any chance of extension or modification in the protocol of the study will be notified to the committee for prior approval.

Consent forms should be retained for future references.

We will appreciate if committee is kept abreast with the quarterly progress of the study.

You may proceed with the study subject to the provision of periodic reports.

Thank you,

19.11.12

Farzana Amir,

Chair person, Ethics Committee

Tabba Heart Institute,

Tabba Heart Institute

APPENDIX 10: Study Protocol Presentation at Third International eHealth Conference 2012 Pakistan (21 – 22 January, 2012)

e Health
HAP Association of Pakistan

eHealth Association of Pakistan

Acknowledges the Scientific Paper Presentation by

Dr. Javed Ismail

Titled

The utility of mobile phone in the prevention of cardiovascular events, through lifestyle modification - a prospective, randomized, controlled, multicenter clinical trial, in Karachi, Pakistan

at the

Third International eHealth Conference 2012

"Road to National eHealth Strategy for Pakistan"

University of Health Sciences, Lahore, Pakistan
January 21-22, 2012

Dr. Haroon Roedad Khan
President

Dr. Azeema Fareed
Vice President

Dr. Hammad Durrani
General Secretary

APPENDIX 11: Abstract Presented at 3rd eHealth Conference 2012, Pakistan

Investigators:
Javed Ismail, Hosen Kiat, Esben Strodl, Junaid Ansari, Jun Ma, Andrew Sindone, Shariq Khoja, Dylan Kelly

TITLE: The utility of mobile phone in the prevention of cardiovascular events, throughlifestyle modification - a prospective, randomized, controlled, multicenter clinical trial, in Karachi, Pakistan.

INTRODUCTION: Preventive strategies (primary and secondary) to reduce burden of cardiovascular disease have been met with limited success due to the cost and difficulty in healthcare delivery. Mobile phone text messaging (SMS/MMS/Voice messages) demonstrates strong potential as a tool for health care improvement.

OBJECTIVE: To assess the effectiveness of lifestyle modification messages delivered by SMS/MMS/Voice mail to patients following non-fatal cardiac events in reducing future hospitalizations, nonfatal and fatal cardiovascular events, as well as all-cause mortality.

METHODOLOGY:
It is a Prospective, Multicenter, Randomized, Controlled clinical trial. The patients hospitalized with their first cardiac event (nonfatal MI, CABG, PCI, unstable angina) will be recruited from the participating tertiary care cardiac specific hospitals – the Karachi Institute of Heart Disease Tabba Heart, and the National Institute of Cardiovascular Diseases in Karachi, Pakistan. We allocate each participant to either the intervention group, i.e. those who will receive behavioral change/life style modification education through mobile phone, or to the usual standard of care group (non-intervention group). The patient allocations were carried out through permuted block randomization to ensure a balance in the patients to each group. The participants were requested to nominate a *carer* (close relative or friend) who are the persons responsible for taking day-to-day care of the patients at home. A free and open source software called 'FrontlineSMS' will be used for sending SMS messages, while the medical records of participants will be stored using a community-based electronic medical record system called 'OpenMRS'. Both these systems will be integrated for the flow of information.

Based on power analysis a total of 1540 patients (770 in the intervention and 770 non-intervention groups) and their respective *carers* (n: 1540 as well) will be enrolled over 12 to 16 months. All patients will be followed up for a minimum of 6 to 9 months (range 21 to 6 months).

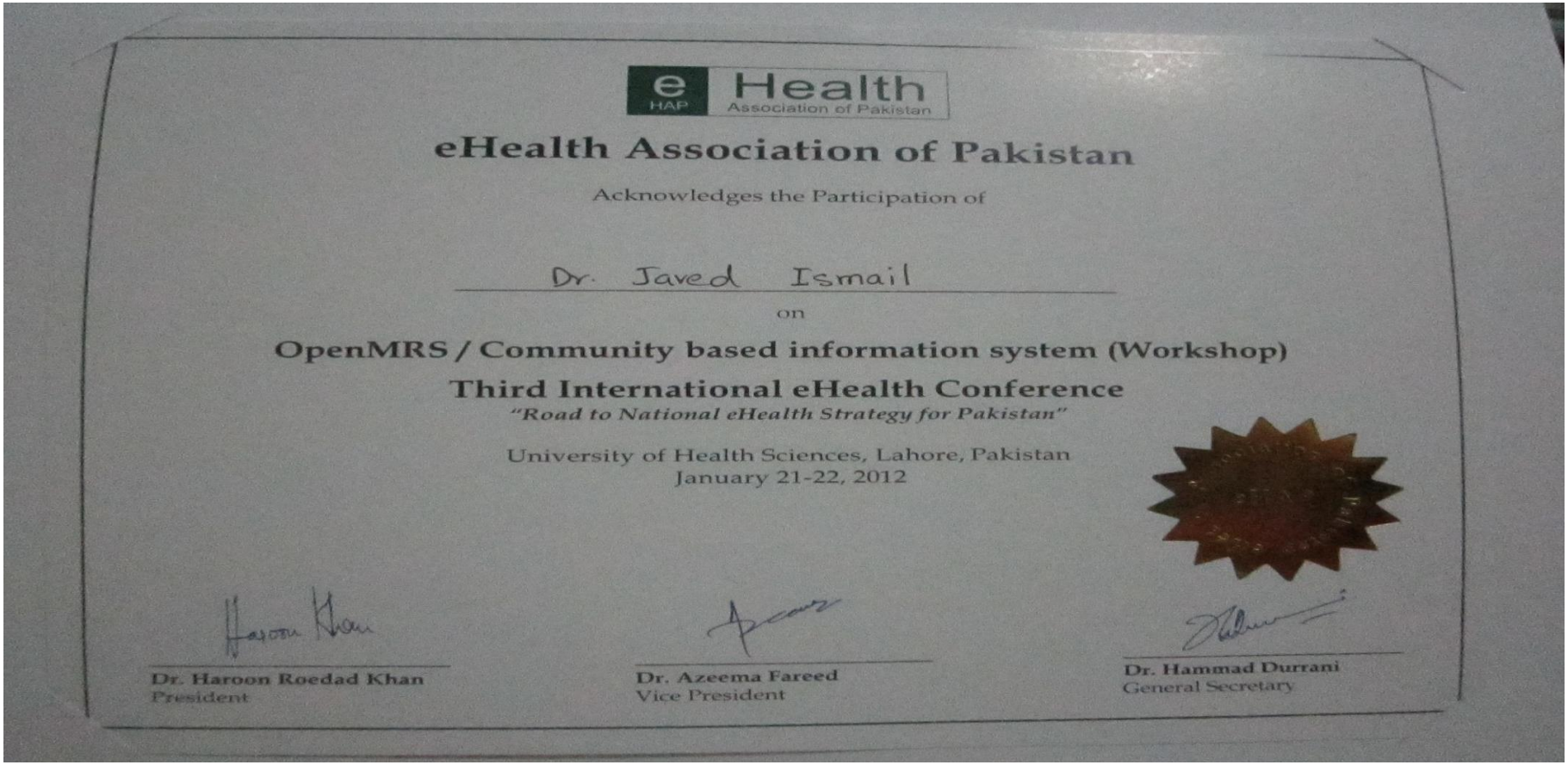
A regular mobile phone messages (SMS/MMS/Voice mail) regarding lifestyle modification will be delivered to patients of intervention group (Secondary prevention) and one of their carer. The mobile phone message based rehabilitation program will be structured according to the latest guidelines developed by the WHO for the prevention of cardiovascular disease.

Blood samples will be drawn to investigate lipid profile, HbA1c, blood sugar, and urinary urea creatinine etc at regular designated intervals.

KEY WORDS: Cardiovascular diseases, Mobile phone, SMS, Rehabilitation, Lifestyle modification

NOTE: Interim analysis till January 2012 will be shared in the conference

APPENDIX 12: Attended workshop on OpenMRS/Community based information system at 3rd International eHealth Conference Jan. 2012, Pakistan



eHAP Health Association of Pakistan

eHealth Association of Pakistan

Acknowledges the Participation of

Dr. Javed Ismail

on

OpenMRS / Community based information system (Workshop)

Third International eHealth Conference

"Road to National eHealth Strategy for Pakistan"

University of Health Sciences, Lahore, Pakistan
January 21-22, 2012

Dr. Haroon Roedad Khan
President

Dr. Azeema Fareed
Vice President

Dr. Hammad Durrani
General Secretary

APPENDIX 13: Pilot Study presentation focusing on Psychological component of the study at 7th Liaquat National Hospital and Medical College Symposium (24 – 26 February, 2012)

LIAQUAT NATIONAL HOSPITAL AND MEDICAL COLLEGE
INSTITUTE FOR POSTGRADUATE MEDICAL STUDIES & HEALTH SCIENCES

7th LNH Symposium
24th to 26th February 2012

Chairman:
Dr. Shakil Aqil

Co-Chairman:
Dr. Syed Ali Arsalan

Secretary:
Dr. Salman Sharif

Special Advisors:
Dr. Abdul Mannan
Prof. Amir Ali Shoro

Scientific Committee:
Dr. Rufina Soomro/ Dr. S. M. Nadeem/ Dr. Saeed Akhtar / Dr. Kunwar Naveed
Plenary Session:
Dr. Aziz Abdullah/ Dr. Faisal Ahmed/ Dr. Tauqir-Ul-Islam/ Dr. Tahira Parveen
Publication Committee:
Dr. Zehra Naqvi/ Dr. Mansoor-ul-Haq/ Dr. Amna Khursheed/ Dr. Furqan Ali Siddiqui/ Dr. Zia Rizvi
Workshops Committee:
Dr. Naveen Faridi/ Dr. Moinuddin/ Dr. Murtaza/ Dr. Saleha Anwar
Awards:
Dr. Haleema Hashmi/ Dr. Khalid Imam/ Dr. Lubna Kamani/ Dr. Misbah Tahir/ Dr. Sellal Ahmed
Registration:
Dr. Mohammad Arshad/ Dr. Junaid Alam/ Dr. Qurat-ul-Aman/ Dr. Jafar Imam/ Dr. Farhat Begum
Finance:
Dr. Shahid Noor/ Dr. Zahid Habib/ Dr. Yasmin Bhurgari/ Dr. Hatim Ali Shah
Medical College:
Dr. Javed Altaf Baig/ Dr. Nazeer Solangi/ Dr. Khursheed Hashmi/ Mr. Sultan Ahmed/ Dr. Naseer Balouch
Paramedical Affairs:
Mr. Hasan Abbas/Ms Alia Nasir/ Mrs. Roselean Joseph/ Mr. Nasir Mansoor
Social Events:
Dr. Nighat Abbas/ Dr. Salma Batool/ Dr. Ali Abbas/ Dr. Kashif Abbas/ Dr. Tabassum Zehra
Audiovisual:
Dr. Intikhab Taufiq/ Dr. Saeed Mahar/ Dr. S. M. Irfan/ Dr. Amir Saghir/ Dr. Abdul Hameed
Press & Media:
Dr. Ishrat Saleem/ Dr. Nadeem Naqvi/ Dr. Faisal Siddiqui/ Dr. Azra Zafar/ Dr. Mir Saleem
Reception:
Dr. Moiz Sadiq/ Dr. Ayesha M. Qureshi/ Dr. Faiz M. Shaikh/ Dr. Shamim Ahmed/ Dr. Nighat Ejaz
BLS / Skills Lab:
Dr. Shabbir Hussain/ Dr. Mabroor Bhatti/ Dr. Kehkashan/ Dr. Mahmood-ul-Haq
Debate:
Dr. Mashoor Alam/ Dr. Iqtidar Taufiq/ Dr. Kamal Yousuf
Transport:
Dr. Ahmed Asif/ Dr. Zafar Ahmed/ Dr. Kamal Ahmed
Web:
Dr. Shahab Ghani/ Dr. Aamir Riaz/ Dr. Jawaid Iqbal
Marketing Committee:
Dr. Zaki Idrees/ Dr. Sabahat Tariq/ Dr. Feroza Saleem/ Dr. Roomi Mehmood/ Dr. Farzana Adnan/ Dr. Israr Nasir
Medical Education Committee:
Dr. Imran Ghayoor/ Dr. Turab Pishori/ Dr. Saleh Soomro/ Dr. Samina Shamim/ Dr. Rafiq Soomro
Banquet and Meals:
Dr. Ata-ur-Rehman/ Dr. Mohammad Sirajuddin/ Dr. Bushra Rehan/ Dr. Faiza Rizwan
Video Conference:
Dr. Shehab Afzal Beg/ Dr. Naila Zahid/ Dr. Ayesha Chandna/ Dr. Naila Asif
Exhibition:
Dr. Ayub Mansoor/ Dr. Nadeem Khurshaidi/ Dr. Murad Zafar Mari/ Dr. Naveeduddin Ahmed Dr. Shagufta Tahir
Gift & Souvenirs:
Dr. Rizwan Memon/ Dr. Khalid Bhamba/ Dr. Chandar Manglani/ Dr. Saira Naz
Management Support:
Brig. (Retd.) Dr. Syed Naseem Ahmed/ Mr. Akberally Amirally/ Dr. Kashif Ahmed Khan/ Dr. Shehzad Pasha/ Ms. Umaimah Muzammil/ Ms. Kiran Akhtar/ Ms. Farina Parekh Major (Retd.) Nadeem Raja

16th, February, 2012

Dr. Javed Ismail
Karachi institute of Heart Diseases Karachi

Subject: **Confirmation of Oral Scientific Paper Presentation at 7th LNMC Symposium**

Dear Dr. Javed:

Liaquat National Hospital & Medical College, Karachi is holding its 7th Symposium in February 2012.
It is my immense pleasure to invite you on behalf of Liaquat National Hospital & Medical College to present your paper in the in the **Psychiatry** Scientific Session Sunday, February 26th, 2012 from 11:00 am to 1:30 pm.on the Topic **Prevalence of depression and anxiety in patients with first ever cardiac event, admitted in Karachi Institute of Heart Disease.** Your allotted time will be 8 minutes.
This is remained you that registration is mandatory for participation in the symposium.

Kindly confirm your participation in this program.

Regards,

Dr. Rufina Soomro
Chairman Scientific Committee
7th LNH Symposium
Liaquat National Hospital & Medical College

LIAQUAT NATIONAL HOSPITAL, NATIONAL STADIUM ROAD, KARACHI- 74800 PAKISTAN
SYMPOSIUM SECRETARIAT TEL: 92-21- 34412500 - 34412511 FAX: 92-21-34140014
Email: 7lnhsymposium@gmail.com Web: www.lnh.edu.pk/symposium2012.php

APPENDIX 14: Letter of Participation at 7th LNH Symposium

LIAQUAT NATIONAL HOSPITAL
INSTITUTE FOR POSTGRADUATE MEDICAL STUDIES
AND HEALTH SCIENCES

To,
Javed Ismail,
Karachi Institute of Heart Disease,

Subject: **Letter of Thanks**

Dear sir/madam

On the behalf of deptt of mental health we would like to say thanks for your participation in LNH symposium.

Thank you again and we hope that you will be participating in future program as well.

You're truly,

27/2/17

DR.Ayesha.Muqeem.Quraishy
Consultant psychiatrist (HOD)
Liaquat National Hospital

NATIONAL STADIUM ROAD, KARACHI-74800, PAKISTAN. Tel: 92-21-34939612, Fax: 92-21-34140014
UAN : 111-456-456, Email: admin@lnh.edu.pk Website: www.lnh.edu.pk

APPENDIX 15: Abstract of Pilot study Presented at 7th LNH Symposium

Prevalence of depression and anxiety in patients with first ever cardiac event, admitted in Karachi Institute of Heart Diseases (KIHD).

Javed Ismail*, Sidra Maqbool¥, Rabbia Parvez¥, Zara Saeed¥, Yusra Aghai¥, Sidra Amjad¥, Junaid Ansari*, Esben Strodl§, Hosen Kiat$
* Karachi Institute of Heart Diseases, Karachi, ¥ 3rd Yr. MBBS student Dow Medical College, DUHS, § Queensland University of Technology, Australia, $ Macquarie University, Sydney Australia.

BACKGROUND
Depression and anxiety are psychological disorders known to be prevalent in cardiac patients. To the best of our knowledge no data exist for our population.

OBJECTIVE
To find out the prevalence of depression and anxiety in patients with first ever cardiac event, admitted in KIHD.

METHOD
This cross-sectional study was conducted on patients with first ever cardiac event at KIHD over a period of two months. We interviewed 306 consented patients, and administered a standardized questionnaire to collect information regarding socio-demographics and cardiac risk factors. Symptoms of depression and anxiety were evaluated through validated Patient Health Questionnaire (PHQ 9) and Generalized Anxiety Disorder Assessment (GAD 7).

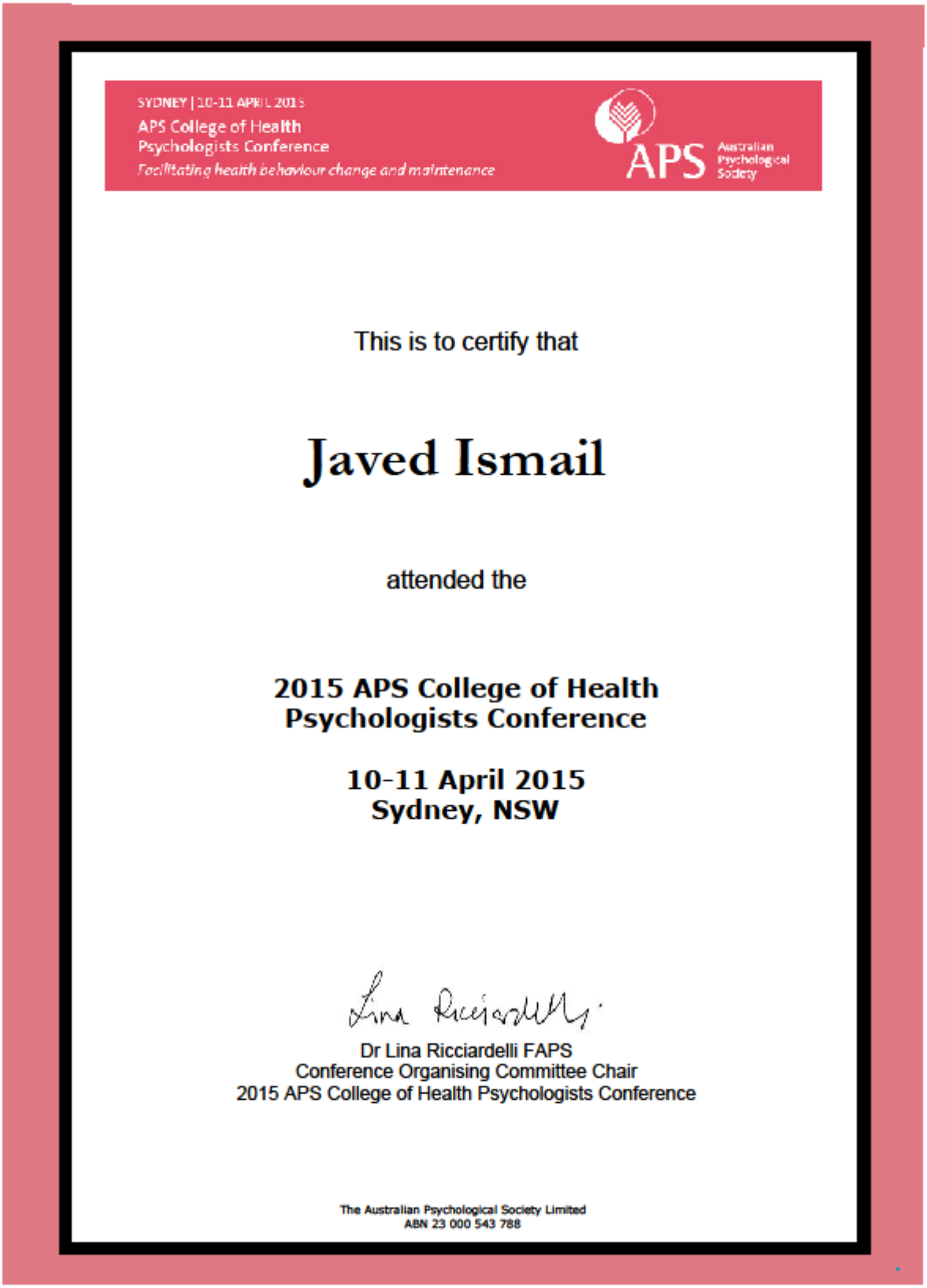
RESULT
Out of 306 subjects, 199(65%) were male and the mean age was 53.31 years. There were 101(33%) and 165(53.9%) patients of diabetes mellitus and hypertension respectively. There were 88(28.8%) smokers and 218(71.2%) were not engaged in exercise. Parents of 48(15.7%) of patients had consanguineous marriage. A total of 180(58.8%) had myocardial infarction out of which 71(23.2%) had NSTEMI. There were 84(27.5%), 38(12.4%) and 18(5.9%) patients suffering from mild, moderate and moderately severe depression respectively whereas 13(4.2%) were afflicted by severe depression. Severe anxiety was found in 24(7.8%) while 81(26.5%) and 53(17.3%) had mild and moderate anxiety respectively.

CONCLUSION:
Our research concludes that there is a rising incidence of depression and anxiety in cardiac patients which could be attributed to their disease. More studies should be conducted to evaluate these disorders.

KEY WORDS
Depression, Anxiety, Cardiovascular Disease, PHQ-9, GAD-7.

APPENDIX 16: Study Protocol Presentation at 5th Annual Dr. Abdul Haque Khan Memorial International Cardiology Symposium (1st – 3rd June, 2012)

APPENDIX 17 :Oral Presentation of Study "Mobile Phone Assisted Psychological Well-Being for The Prevention Of Coronary Heart Disease" At Australian Psychological Society College of Health Psychologist Conference Sydney, Australia, 2015 (10 – 11 April, 2015)



SYDNEY | 10-11 APRIL 2015
APS College of Health Psychologists Conference
Facilitating health behaviour change and maintenance

APS Australian Psychological Society

This is to certify that

Javed Ismail

attended the

2015 APS College of Health Psychologists Conference

10-11 April 2015
Sydney, NSW

Dr Lina Ricciardelli FAPS
Conference Organising Committee Chair
2015 APS College of Health Psychologists Conference

The Australian Psychological Society Limited
ABN 23 000 543 788

APPENDIX 18: Abstract presented at APS College of health psychologist conference Sydney, Australia, 2015

Mobile phone-assisted psychological well-being for the prevention of coronary heart disease

ISMAIL, J., (Macquarie University), KIAT, H., (Macquarie University), STRODL, E., (Queensland University of Technology), ANSARI, J. A., (Karachi Institute of Heart Diseases, Pakistan), MA, J., (Macquarie University), SINDONE, A. (Concord Hospital, NSW), KHOJA, S. (The Aga Khan University, Pakistan), & KLEIN, A. (University of Sydney)

Cardiovascular disease is the leading cause of deaths globally, especially in South Asian countries. Coronary Heart Diseases (CHD) has a high prevalence in Pakistan and is a major cause of mortality in this country. Psychological factors such as depression and anxiety are among the major contributing modifiable risk factors. Text messaging may be a preventive tool in reducing psychological distress among CHD patients and healthy care givers. This study aimed to explore the effectiveness of a text messaging intervention for improving the mental and physical health of patients with CHD presenting at hospitals in Pakistan. A randomized controlled single blinded clinical trial was conducted in 3 cardiac specific tertiary care hospitals in Pakistan. Participants were first ever survived patients of CHD and their nominated healthy care givers. Three thousand two hundred thirty one participants (2650 patients, and 581 care givers) were randomized in intervention (text messaging) and non-intervention group. Validated Urdu version of PHQ9 and GAD7 was implemented at baseline and at every subsequent follow-ups. Positive psychological wellbeing motivational text messages were sent twice weekly to the intervention group. The major findings of this study will be presented including prevalence of psychological morbidity in this population, as well as the outcome of the trial. The implications of these findings for implementing text messaging with CHD patients will then be discussed.

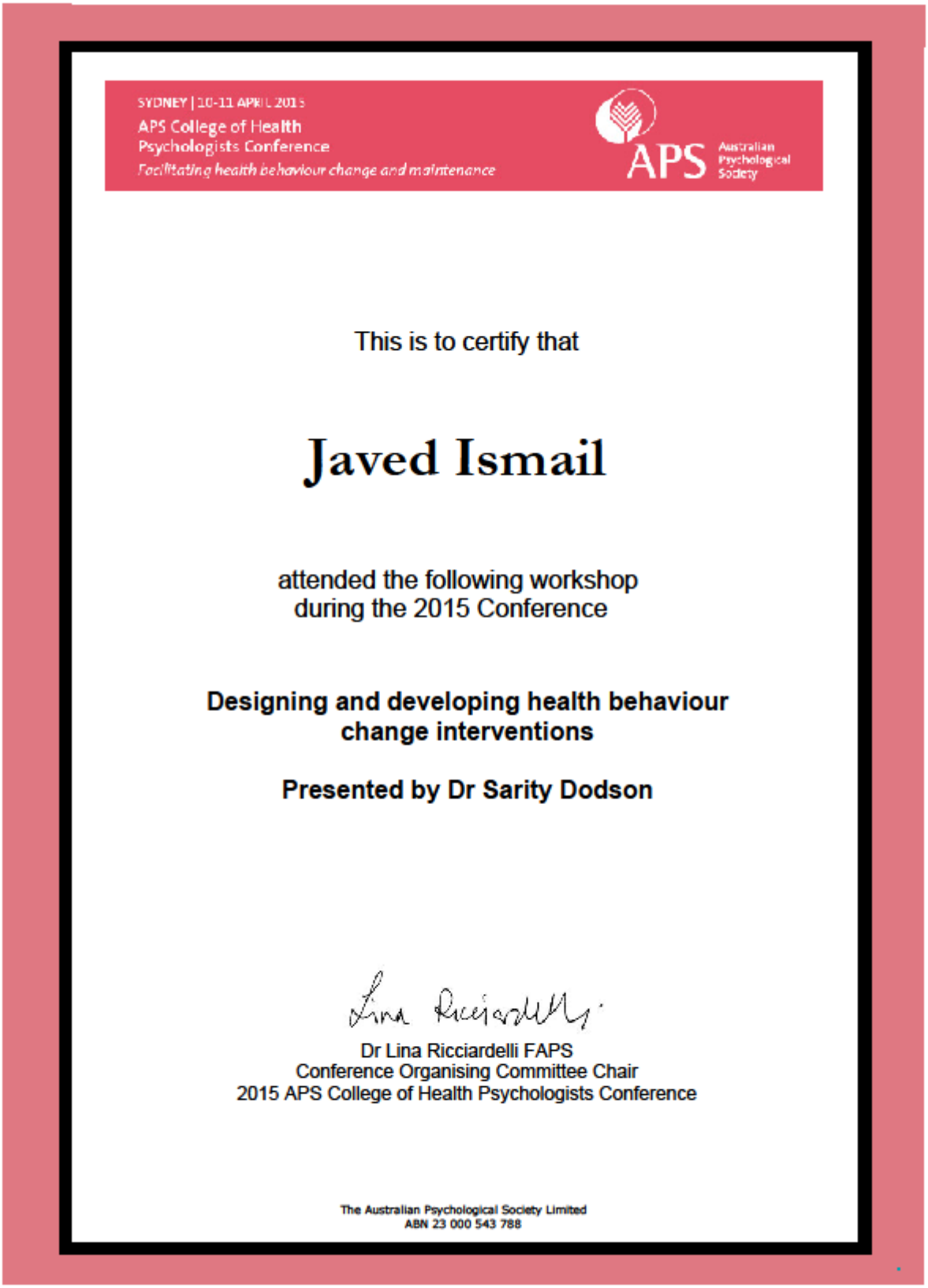
Can we stress healthier? Initial findings comparing stress mindset to stress appraisal

KILBY, C. (Department of Psychology, Macquarie University), & Sherman, K. (Centre for Emotional Health, Macquarie University; Westmead Breast Cancer Institute)

Christopher.Kilby@mq.edu.au

Stress mindset, a trait heuristic, claims that positive stress beliefs lead to more successful coping strategies than negative beliefs. This is similar to the Cognitive-Phenomenological model detailing stress appraisals which evaluate how challenging (positive) and threatening (negative) a stressor is perceived by an individual. The aim of this online experiment was to outline the relationship between stress mindset and stress appraisals. Participants (N=124) initially completed measures assessing lifetime and perceived stress, trait anxiety, mathematic self-efficacy and stress mindset. They were then randomly allocated one of two sets of instructions regarding a stressful mathematics task framed as either threatening or challenging. Participants completed post-manipulation stress mindset and stress appraisals measures. Both groups then completed an identical mathematics task. Post-manipulation stress mindset scores did not differ between instruction sets. As predicted, pre-manipulation stress mindset scores predicted post-manipulation stress mindset scores B=.874, p<0.0005, supporting the claim that stress mindset is a heuristic. Post-manipulation stress mindset was, as predicted, weakly associated with challenge B=.286, p=.002, but not threat appraisals. This association suggests the two models are independent, yet related. These findings warrant a longitudinal investigation of causality to understand how stress mindset functions to improve coping in the context of the Cognitive-Phenomenological model.

APPENDIX 19: Attended Workshop on Designing and developing health behaviour change interventions at APS college of health psychologist conference, Sydney Australia, 2015



SYDNEY | 10-11 APRIL 2015
APS College of Health Psychologists Conference
Facilitating health behaviour change and maintenance

APS Australian Psychological Society

This is to certify that

Javed Ismail

attended the following workshop
during the 2015 Conference

Designing and developing health behaviour change interventions

Presented by Dr Sarity Dodson

Dr Lina Ricciardelli FAPS
Conference Organising Committee Chair
2015 APS College of Health Psychologists Conference

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APPENDIX 20: Oral Presentation of Study "Mobile Phone Assisted Psychological Well-Being for The Prevention Of Coronary Heart Disease" at Inter-university Neurosciences and Mental Health Conference (24th Sep. – 25th Sep. 2015). University of New South Wales, Sydney Australia.

Day 1: Thursday 24 September 2015		
PARALLEL SESSIONS		
	Session 3: PTSD, Stress and Anxiety **Location: Leighton Hall** **Chair: Dr Chris Dayas, School of Biomedical Sciences & Pharmacy, The University of Newcastle**	**Session 4: Learning and Memory** **Location: The Galleries** **Chair:**
13:45	***Stress and the New South Wales Police Force: The prevalence of various coping mechanisms*** **Jaymen Elliott** School of Life Sciences, UTS	***Learning and choice in a complex and dynamic world*** **Thomas J Burton** School of Medical Sciences, The University of Sydney
14:00	***Childhood interpersonal trauma exposure is associated with enhanced electrophysiological responses to threat faces in adults with PTSD*** **Denise Chu** Department of Psychiatry, The University of Sydney; Brain Dynamics Centre	***Upregulation of cortico-cerebellar functional connectivity after motor learning*** **Tjeerd W. Boonstra** Black Dog Institute; UNSW
14:15	***Predicted vs. random chronic stress, effects on cell morphology and learning and decision based behaviour*** **Steve Kassem** The Brain and Mind Research Institute, The University of Sydney	***Using peripheral electrical stimulation to increase brain excitability and enhance the rate of motor learning*** **Simon John Summers** School of Science and Health, Western Sydney University
14:30	***Inhibition of the α9α10-nACh receptor: Good pain relief or a side effect liability?*** **Sarasa A. Mohammadi** School of Medical Sciences, The University of Sydney	***Timing in taste aversion learning: When is interference most effective?*** **Dorothy Kwok** The University of Sydney
14:45	***Impaired fear extinction retention following consumption of high fat high sugar diet during adolescence*** **Amy C Reichelt** School of Psychology, UNSW	***Deconstructing episodic memory processes in the dementias*** **Muireann Irish** School of Psychology, UNSW; NeuRA
15:00	***For whom the fear returns: Individual differences in relapse*** **Gabrielle King** UNSW	***Use of a maze test to evaluate disease progression in Merino sheep with neuronal ceroid lipofuscinosis*** **Imke Tammen** Faculty of Veterinary Science, The University of Sydney
15:15	***Cortical perineuronal nets, parvalbumin neurons, and fear inhibition in adolescent rats*** **K.D. Baker** School of Psychology, UNSW	***Differential associations between quantitative electroencephalogram markers and memory performance in mild cognitive impairment: influence of obstructive sleep apnea*** **Nathan Cross** Brain and Mind Centre; Woolcock Institute of Medical Research, The University of Sydney
15.30	***Mobile phone-assisted psychological wellbeing for the prevention of coronary heart disease – randomized clinical trial*** **Javed Ismail** Macquarie University	***Understanding the gain of function ADNFLE mutations in heteromeric α4β2 neuronal nicotinic receptors*** **Dinesh C. Indurthi** Faculty of Pharmacy, The University of Sydney
15.45 - 16.15 pm	Afternoon tea	
PLENARY SESSION - Leighton Hall, The John Niland Scientia building, UNSW		
16.15 – 17.15 pm	**Closing plenary day 1:** ***Hypothalamic CRH neurons control behavioural choice following stress*** **Professor Jaideep Bains**, Hotchkiss Brain Institute, University of Calgary, Canada	
17.15 - 18.15 pm	Drinks available in the Tyree Room Poster presentations	

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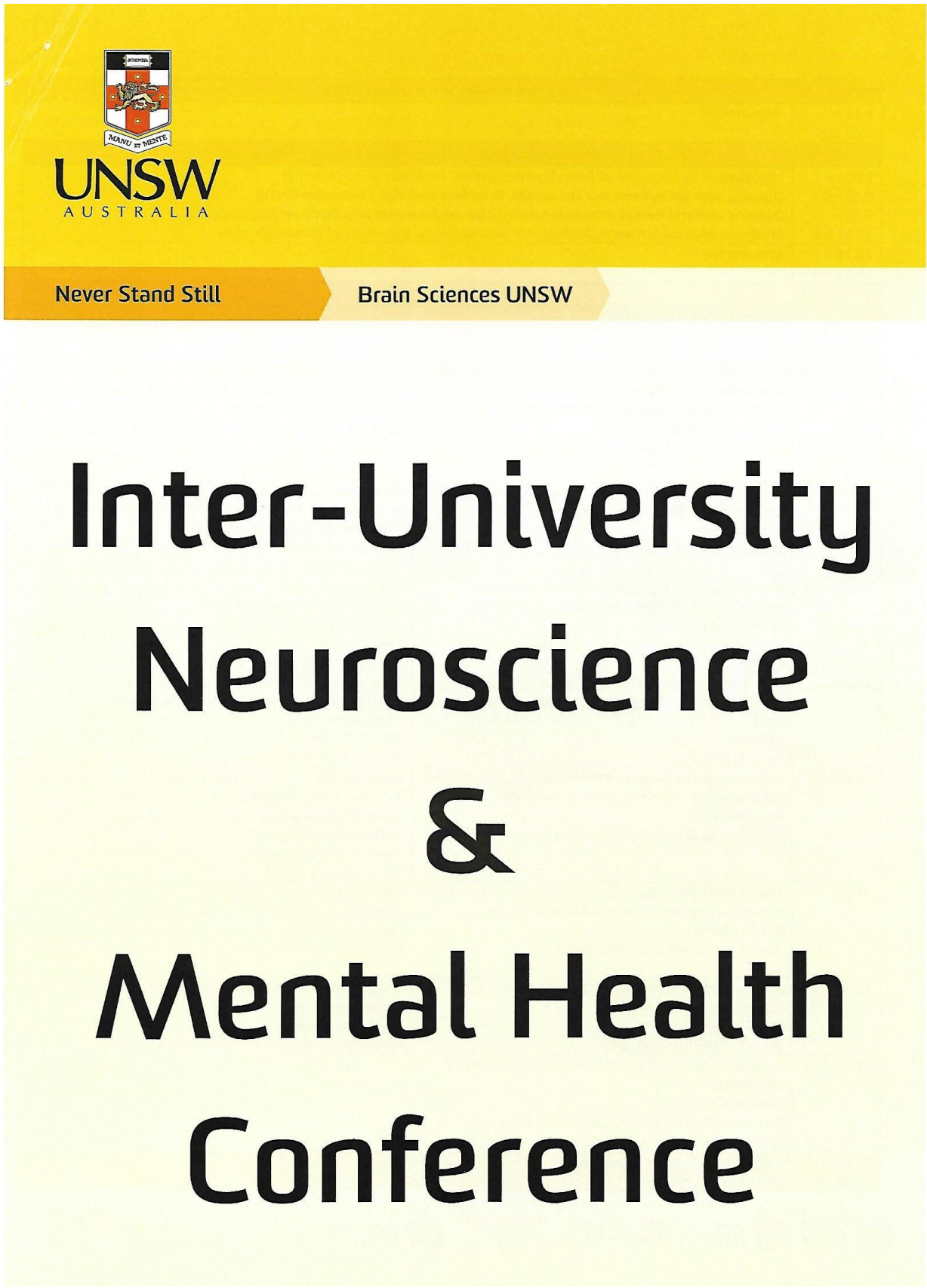
APPENDIX 21: Inter-university Neurosciences and Mental Health Conference Program.



APPENDIX 22: Abstract presented at Inter-university Neurosciences and Mental Health Conference.

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Mobile phone-assisted psychological wellbeing for the prevention of coronary heart disease – randomized clinical trial

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[5.] *Director, Tabba Heart Institute, Karachi Pakistan,*
[6.] *Prof. Medicine, Macquarie University Hospital, NSW*

Background: Psychological factors, like depression and anxiety are among the major contributing modifiable risk factors for the development of coronary artery disease (CAD).
Text messaging may be a preventive tool in reducing psychological distress among CHD patients and healthy care givers. This study aimed to explore the effectiveness of a text messaging intervention for improving the mental and physical health of patients with CHD.

Methods: A prospective, randomized, clinical trial was conducted in 3 cardiac specific tertiary care hospitals in Karachi, Pakistan. Participants were patients who had their first cardiac events and their respective nominated care-givers. Patients and their care-givers were randomized into two groups, intervention (IG) or usual care group without intervention (NIG). Research assistants, recruiting the subjects were blinded to the IG or NIG. Validated Urdu version of PHQ9 and GAD7 was implemented at baseline and at every subsequent follow-ups. Positive psychological wellbeing motivational text messages were sent twice weekly to the intervention group.

Results: Analysis revealed that motivational psychological wellbeing SMS messages through mobile phone does not have any significant effect in reducing depression and anxiety among intervention group as compared to non-intervention group. Although female were more depressed and anxious in both group, but trend remain the same till the end of study.

Conclusions: SMS text messaging alone to improve psychological wellbeing was not effective. Keeping in view of the experiences gained from this study, future study with short term face to face motivational sessions with support of long term SMS text messaging is recommended.