

An Exploration of the Psychological Indicators of Aspirin Adherence, in Patients with Stable Coronary Artery Disease, using a Direct Assay Measurement.

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**AN EXPLORATION OF THE PSYCHOLOGICAL
INDICATORS OF ASPIRIN ADHERENCE, IN PATIENTS
WITH STABLE CORONARY ARTERY DISEASE, USING
A DIRECT ASSAY MEASUREMENT.**

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A thesis submitted to the population of health science,
RCSI, in fulfilment of a Masters through research.

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Professor Dermot Kenny and Professor David Foley.

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AN EXPLORATION OF THE PSYCHOLOGICAL INDICATORS OF ASPIRIN ADHERENCE, IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE, USING A DIRECT ASSAY MEASUREMENT.

ABSTRACT

Background-Although prescribed to approximately 90% of persons with cardiovascular disease (CVD), it is estimated that adherence to aspirin therapy is only approximately 70%. Established psychosocial predictors of adherence include patient beliefs about medicines and illness, depression and social support. However, no study has assessed these simultaneously to determine the best predictor of adherence when using an objective measure of aspirin adherence.

Method-After ethical approval was received we surveyed 106 patients with cardiovascular disease from Beaumont Hospital who participated in a study of aspirin effectiveness in patients with stable coronary artery disease using a direct assay measurement (thromboxane B2). The following measures were used to assess the psychological predictors of adherence: Beliefs about Medicines Questionnaire, Brief Illness Perception Questionnaire, Patient Health Questionnaire-2 and ENRICHD Social Support Inventory. These were administered either by post or by interview to patients who were willing and able to consent for the current sub-study. Data was amalgamated with the initial study and analysed to determine the best predictors of aspirin adherence.

Results-There was a 56% response rate to the survey (n=106). The mean age was 63 years; 66% had an effective response and 34% had an ineffective response (defined as serum thromboxane B2 levels of greater than 2.2ng/ml). There was no significant correlation between psychological adherence predictors and thromboxane level or self-reported non-adherence.

Conclusion-Although most psychological variables correlated significantly with each other as expected, no psychological variable was associated with thromboxane level or self-reported adherence. Patients who had higher weight and alcohol consumption were significantly more likely to be non-adherent as measured by thromboxane.

CHAPTER 1- General Introduction and adherence

Introduction

Cardiovascular disease (CVD) is the single largest cause of death in Ireland (1), and age-standardised death rates here are significantly higher than other European Union¹⁵ (EU15) States (1). CVD is the major cause of death in women in all European countries; below 75 years, 42% of women die from CVD compared with 38% of men (2). According to Versteeg et al. (3), low socio-economic status, lack of social support, stress at work and in family life, depression, anxiety, hostility, type D personality and behaviours contribute both to the risk of developing CVD and the worsening of the clinical course and prognosis of CVD (3). These factors act as barriers to treatment adherence and efforts to improve lifestyle, as well as to promoting health and wellbeing in patients and populations (4). Our understanding of the reasons for changes in the behaviour of both populations and individuals remains incomplete, and the mechanisms whereby such changes in behaviour translate into changes in disease patterns are not completely understood (4). Patients with CVD are prescribed an extensive range of medications to reduce their risk of (recurrent) acute cardiovascular events. The Fourth Joint Task Force on cardiovascular disease prevention recommends a number of populations should take preventive medication (5):

- those with established CVD
- those at high risk for CVD, and their immediate family members.

The Fifth Joint Task Force describes how in long-term secondary prevention after myocardial infarction, stroke, or peripheral arterial disease (PAD), aspirin is the most studied drug. In a meta-analysis of 16 trials comprising 17,000

individuals, the Antithrombotic Trialists' Collaboration, 2009 (6, 7) found that allocation to aspirin was associated with serious vascular events in 6.7% of patients per year compared to 8.2% of controls. The risk of total stroke was 2.08% per year compared to 2.59% ($P = 0.002$) and coronary events 4.3% per year compared to 5.3% ($P = 0.0001$). Aspirin was associated with a 10% reduction in total mortality (RR 0.90, 95% CI 0.82–0.99), but was also associated with a significant excess of major bleeds; nevertheless, the benefits of aspirin exceeded the bleeding hazards. Few drugs have demonstrated similar efficacy with up to 50 major vascular events avoided per 1000 patients treated per year, therefore aspirin has been recommended for persons with CVD as it is one of the most effective therapies (8).

In Ireland, there has been a 4-fold increase in CVD medication prescription since 2000 (9). However, the results of EUROASPIRE III demonstrated that the secondary prevention profile of those with CVD was suboptimal (9). In the EUROASPIRE surveys, blood pressure management showed no improvement over the three surveys that were carried out over a 12 year period, despite increases in prescriptions for all classes of anti-hypertensive drugs. One explanation given for this finding is the rising proportion of overweight and obese patients. Other reasons were low dose prescriptions, inadequate titration of doses and poor patient adherence to their anti-hypertensive medication (9). A recent systematic review by Chowdhury et al. (10) where they looked at adherence to cardiovascular therapy and the clinical consequences, showed overall 60% of patients had good adherence (more than or equal to) $\geq 80\%$ to cardiovascular medications. They concluded

that approximately 9% of all cardiovascular events in Europe could be attributed to poor adherence to cardiovascular medications alone. This study also showed a rate of only 70% of aspirin adherence. This figure appears to be supported by a recent study on the use of secondary prevention drugs in patients with an indication for aspirin therapy, investigators found that approximately only 25% of patients were actually taking it although the measurement of adherence appears to be mainly through self reporting. They found that rates of adherence were higher in high-income countries 62% compared to low-income countries 9%, and point out that compliance is a necessity prior to platelet function testing (8, 11, 12). A recent study by O'Carroll et al. (13) funded by the Scottish Government looking at secondary prevention of stroke with Aspirin therapy, describes the importance of a valid and reliable measurement of adherence as patients may respond in a way that is socially desirable and over report adherence. They used urine measurements of salicylate levels as an objective measure but found no significant difference between the levels of aspirin takers and non-aspirin takers which raised concerns of the sensitivity of the assay. Therefore the assay was not used as a measure of adherence in their final analysis.

A previous study looking at the role of weight and enteric coating on aspirin response in cardiovascular patients has shown the thromboxane B2 ELISA assay a reliable measure in detecting aspirin ingestion and adherence, therefore this was the objective measure chosen for the current study (11). In this study they found 19% of patients were not responsive to their aspirin but when questioned by a nurse, half admitted to non-adherence and the other half were found to be responsive when observed ingesting their daily dose of

aspirin showing a possible resistance in only 1%. Recent researchers have also found this assay a reliable tool in cardiovascular patients with diabetes (14). Chowdhury et al. (10) advises that measures to enhance adherence are urgently required to maximise the effect of cardiac therapies pointing out that poor adherence is a worldwide problem that is diagnosable and treatable. They also state that cardiovascular medications such as statins, anti-hypertensives and anti-thrombotics including aspirin, remain the most common medical interventions worldwide for both primary and secondary prevention of cardiovascular diseases.

The next section will review the topic of adherence and the use of thromboxane B₂ assay. Chapter 2 and 3 will review beliefs about medicines and beliefs about illness in the context of their importance for aspirin adherence. Chapters 4 and 5 will review depression and social support and the influences they both have on medication adherence. Chapter 6 is a summary of the literature and the present study. Chapter 7 describes the method used. Chapter 8 shows the results of the responders to the psychological questionnaires and the demographics of the patients looking at the correlations between the demographic variables, thromboxane, self-reported adherence and the psychological variables. Finally in Chapter 9, there is the discussion and conclusion of the literature and the current study and the implications for the future regarding research and clinical practice.

Adherence

Definitions and controversies:

Adherence or compliance to a medication regime is generally defined as the extent to which patients take medications as prescribed by their health care provider (10, 14). The word adherence is preferred because compliance suggests that the patient is passively following the doctor's orders and the treatment is not based on an agreement between the patient and physician (15).

Osterberg et al. (14) suggests that both terms are imperfect and uninformative descriptions of patient medication behaviour, and can stigmatise patients in their future relationships with health care providers, labelling patients without considering the possible psychological reasons for non-adherence (14). They also describe how adherence rates are typically higher in patients with acute conditions such as acute Myocardial Infarction (MI) compared with patients with chronic conditions such as heart failure. Adherence in patients with chronic conditions such as heart failure is disappointingly low, typically dropping off dramatically after 6 months (16). Estimates of the extent of non-adherence vary across different studies, largely because of differing methods of, and difficulties in, measuring adherence, and inconsistency in the definitions used for the term 'adherence' (17, 18).

A second definition of adherence considers the duration of time a patient continues with a prescription regimen, even if intermittently, before discontinuing the medication prematurely. With this definition, patients are categorized as non-adherent if they discontinue a medication before a certain time period. Primary non-adherence refers to when a patient "discontinues" a

medication before filling a prescription even once (19, 20). Other authors argue that the cut off for optimal adherence may vary depending on the pharmacokinetic and pharmacodynamic effects of the individual drug and the clinical setting (19).

Most definitions of adherence presume that adherence is a stable patient characteristic, yet Kronish and Ye (19) point out there is evidence that it may be more accurately understood as a dynamic process. They give the example of patients who have suffered an acute coronary syndrome (ACS), where the acute episode can serve as a teachable moment that leads to medication adherence improvement, whereas other patients may have reduced medication adherence due to the stress of the ACS. The review by Kronish and Ye. (19) seems to continually show that while the patient is acute this is a good opportunity to assess and promote adherence while the patient has the support of the multidisciplinary team.

Across the different definitions and settings, it is suggested that around 50% of medicines are not used as intended by the prescriber (21). Medication adherence is estimated to be only approximately 50% for people with chronic conditions, although this estimate varies widely depending on the regimen assessed and the definitions used (22). However, the measurement of adherence can differ between studies and there is little consensus on what constitutes 'good' adherence (e.g. taking medications as prescribed 80% or more of the time – a binary variable; or the proportion of prescribed medications that were actually taken – a continuous variable).

Most clinical trials consider 80% to be adherent but average rates of adherence in clinical trials can be remarkably high owing to the greater attention and selection criteria of patients (23). Kronish and Ye (19) point out that there are gaps in the knowledge of adherence that need to be addressed, stating that researchers commonly use a cut-off point of less than 80% of pills taken as prescribed to define poor adherence to cardiovascular medications. They describe how the optimal cut off points for categorizing adherence remains poorly understood and how this cut off point can be traced back to a small anti-hypertensive trial where the authors found that diastolic blood pressure declined significantly only when participants took more than 80% of their pills (24). There is strong reason to suspect that the optimal threshold for adherence between medications is quite different due to pharmacokinetic and pharmacodynamic properties. In some clinical settings, for example, immediately after coronary artery stenting, the optimal threshold for anti-platelet therapy may be as high as 100%, whereas in other settings where patients are of low cardiovascular risk requiring statins, a clinically relevant threshold for defining adherence may be lower (24). Kronish and Ye (19) suggest that increasing our understanding of the optimal cut off points for adherence in cardiovascular medications may lead to a more precise understanding of the problem, the populations to which adherence interventions should be targeted, and the scale of resources needed for interventions.

Thus, as we can see with the above examples, defining adherence can be problematic and it may be appropriate to measure it in different ways depending on the pharmacodynamics and pharmacokinetics of the type of drug, patients and condition we are interested in monitoring. We can see from the literature and experience that patients who sign up for studies are likely to be more adherent as this is normally part of the inclusion criteria, that patients are willing to adhere to the protocol and medication regime, particularly in randomized clinical trials, therefore patients are “cherry picked”. It is also more unlikely in observational studies that patients who are non-adherent will volunteer for monitoring when they are aware that this will be monitored. Finally, good adherence should be seen as a means of achieving a satisfactory therapeutic result and not as an end in itself, as the patient’s perspective must always be considered (25).

Prevalence and costs of non-adherence:

Poor adherence has a significant human cost in terms of patient safety and quality of life; it also causes a serious problem for health systems in terms of reduced health outcomes, unnecessary treatments and hospitalisations, causing resource waste of prescribed medicines funded by the healthcare system. Low adherence is also connected to the development of resistance which is fast becoming an urgent global problem (10, 26).

It is estimated that there are 194,000 deaths per year in the European Union due to wrong doses and non-adherence of prescribed medication at a cost of 1.25 billion Euros to the economy annually (24). While similar reports estimate medication costs of £12 million due to non-adherence in England in 2004. It is

estimated that £100million each year is wasted on medication dispensed but then returned to pharmacies.

Compared with the amount of resources spent on the development of new drugs, improving patient's medication adherence with their cardiovascular medication has enormous potential for improving health outcomes while reducing healthcare costs (19). Kronish et al. (19) point out that even in clinical trial settings where patients are carefully selected, high rates of poor adherence have been documented and that irrespective of differences in how and when adherence is measured, poor adherence to cardiovascular medications is highly prevalent across patient populations and cardiovascular drug classes.

Poor medication adherence has also been associated with a number of adverse health impacts where, for example, the clinician may be unaware that the uncontrolled risk factor is due to poor adherence. This can then lead to intensification of treatment and the potential for over treatment if the patient suddenly decides to take their complete regimen (27). This can then lead to serious adverse effects for example if a patient's anti-hypertensive medication have been titrated up according to blood pressure readings and then suddenly they decide to take all of the medications as prescribed, this could lead to collapse, organ failure or even death (26).

Poor adherence is also associated with worse health outcomes in several cardiovascular medication adherence studies (10). Rasmussen et al. (28) found that survivors of acute myocardial infarction (MI) who had poor to

intermediate adherence (measured by proportion of days covered <80%) to statins were at 25% and 12% increased risk of mortality compared to survivors with high adherence ($\geq 80\%$). This study also found that advantages associated with improved drug adherence after an acute MI appear to be class-specific and due to drug effects rather than the “healthy adherer” behaviour. Likewise, another study looking at patients that prematurely stopped their thienopyridine anti-platelet medication within 30 days of insertion of a drug eluting stent were 9 times increased risk of mortality in the subsequent year (28, 29). Kronish and Ye. (19) and other authors (30, 31) have found that savings from lower medication costs by patients who may have their medications paid for by an insurer or the state, are offset by increased medical costs which in turn increase overall medical healthcare costs. They suggest that programs to increase medication adherence may actually provide an opportunity for investment in health care services that can improve health outcomes and lower costs. Caulfield et al. (24) suggest strategies to tackle adherence need to take a multi-stakeholder, patient-centred approach.

Adherence is a key priority for future health programmes, reducing unused or improperly used medications is a key factor in improving patient safety and satisfaction and the quality of healthcare while increasing cost effectiveness and chronic disease management. The World Health Organisation has stressed that “increasing the effectiveness of adherence intervention may have a far greater impact on the health of the population than any improvement in specific medical treatments” (24). The authors point out that priority areas with a close link to adherence include the development of

ehealth solutions (32). Lehane and McCarthy (33) point out that a considerable amount of research on this subject from a range of perspectives such as pharmacology, psychology and nursing have shown that health care interventions have not been cost effective or clinically effective in enhancing medication adherence when looking at systematic reviews, the authors also suggest that nurses are in a good position to assess and intervene in improving patient's adherence by understanding the complexities.

Healthy Adherer

Researchers have questioned the extent to which poor medication adherence directly causes worse health outcomes or whether the association between the two is spurious (17, 27). They have speculated that medication adherence is likely a marker of other favourable health behaviours, for example, adherence to medical advice in general or to behaviours like exercise and smoking cessation or socioeconomic characteristics like access to health care or social support. They imply that the strong associations between medication adherence and outcomes are mainly due to a "healthy adherer" rather than to specific benefits of adhering to a particular medication. Evidence that supports the healthy adherer effect comes from several post-hoc analyses of randomized controlled trials in which patients that had better adherence to a placebo, had better health outcomes than patients who were less adherent to a placebo medication. For example, the Beta Blocker Heart Attack Trial showed that patients who were more adherent to placebo had 62% lower odds of mortality than patients who were non-adherent to placebo within a year of follow up (34). These researchers suggest then that if this hypothesis

is correct, then interventions that are directed toward increasing adherence to specific medications may not have the desired effect on health outcomes.

Researchers have suggested another possible explanation for the health benefits of medication adherence is that the act of taking pills may activate a placebo effect (17). Finniss et al. (35) defines the placebo effect as a psychophysiologic effect that is derived from expecting a benefit from treatment. Laboratory studies have shown that the receipt of placebo medications can result in biological effects such as hormonal secretion and immune response. However, studies on the impact of adherence to placebo on health outcomes that adjust for adherence to other health behaviours like smoking and exercise, do not reliably weaken the strength of the benefits of patient's adherence to placebo medication (36).

Kronish and Ye (19) point out that these findings challenge the hypothesis that the benefits of adherence to placebo are due to a healthy adherer effect and increase the likelihood that improved adherence can amplify the biological benefits of the placebo effect.

Further evidence contrary to the "healthy adherer" hypothesis can be seen from Rasmussen et al. (28). This retrospective study of 31,455 elderly Acute Myocardial Infarction (MI) survivors found that poor adherence to statins and rennin-angiotensin system inhibitors post-MI was associated with increased adverse events, whereas poor adherence to calcium channel blockers was

not associated with worse outcomes (a drug class not expected to have an impact on post MI prognosis).

Overall, researchers have concluded that future studies should examine the association between adherence and health outcomes, determining whether the strong association between medication adherence and outcomes is mainly due to a drug effect or whether alternative mechanisms such as “healthy adherer” or placebo effect play a major role. This they suggest can be accomplished by carefully measuring potential confounders of the relationship between adherence and outcomes such as health behaviour, socioeconomic status, or susceptibility for the placebo effect. Researchers are very aware of the placebo effect, and as a result, in cases where there is a recognized strong placebo effect for example with anti-depressants, the drug must show a strong superiority compared to the placebo group in randomized clinical trials. We can see from the literature that medication adherence should be of concern to all groups including physicians, nurses, the multidisciplinary team, carers, patients and the wider community if treatments are going to be therapeutic and cost effective.

Measurements of adherence:

Measurement of adherence can be either indirect or direct. Indirect methods are for example using a self-report where the patient or their relative answers questionnaires or interview questions or use diaries. Direct methods are those that demonstrate drug ingestion using measurement of drug or metabolite in urine or blood (37). Direct methods are less prone to bias, but to date have

not been practical enough to include in large studies of adherence (23). This is likely to be related to costs of the extra man power and labour but also due to lack of patient or end user friendliness. Clinical judgment appears to be the most common way of measuring medication adherence which is generally an indirect measure (19) but studies have shown that clinicians and patients themselves overestimate their adherence (38, 39). A number of self report instruments for measuring adherence have been developed and have the advantage of being brief, inexpensive and can provide immediate feedback to the clinician. However researchers have shown that these scales are at best moderately related to objective measures of adherence and overestimate adherence by 10-20% compared to objective measures (40).

Physiologic or laboratory markers have the advantage of being objective but these are unavailable for all medications and may reflect pharmacodynamics and pharmacokinetics rather than adherence, for example, cholesterol levels with statins and platelet function tests in the case of anti-platelet therapy such as clopidogrel (19). Studies have consistently found that up to 30% of patients are resistant to clopidogrel (41). Pharmacy refill monitoring as outlined earlier has the advantage of being objective and quantifiable in a similar manner to pill counts. Furthermore it is also unobtrusive and inexpensive to obtain from large populations. Unfortunately it is difficult to obtain outside a closed pharmacy system which is not available for all Irish patients, generic refills and over the counter drugs such as aspirin will not always be captured and there is no information if the drug was actually ingested or not (19).

Medication Event Monitoring System-MEMS

MEMS medication bottles contain a microelectronic chip that registers the date and time of every bottle opening (42). This device is currently the gold standard to measure adherence (43) although this assumes that each time the patient opens the lid of the container they are ingesting the medication that is contained in the bottle.

Hugen et al.'s 2002 study (44), "Interventions for helping patients to follow prescriptions for medications assessment of adherence in patients with HIV" looked at the various methods of medication adherence including MEMS, patient report, nurse report and therapeutic drug monitoring. Twenty eight patients were included and the data for twenty six patients was evaluated. According to MEMS data 25% of the patients took fewer than 95% of all doses. Patients self report and therapeutic drug monitoring were significantly correlated with the MEMS data, and the authors point out that the clinical nurse specialist also plays a role in identifying patients who are non-adherent. MEMS has been recognised as not being feasible for use in routine clinical practice due to the high cost but Boogaard et al.'s study (42) was designed to determine the validity of several direct and indirect adherence measures of potential use in resource limited settings.

Electronic medication monitoring, where an electronic chip is attached to the medication blister pack and records when the medication is dispensed from the pack, is also objective and quantifiable, providing a daily pattern of pill taking while also having the possibility of being able to transmit remotely.

They have the disadvantage of being costly and not readily integrated into clinical pathways (17), they also have no advantage for socio-economic factors such as, social support, insurance or financial problems that may be causing the interrupted medication supply (45). In other words, they show us non-adherence but not the reason why.

Assays

Biological assays measure the concentration of a drug or its metabolite and trace compounds in the blood or urine but these measures are often costly and patients who know they will be tested may consciously take medication that they had been skipping, close to the time of the test being administered. Physiological factors and the half-life of the drugs may also have an effect on the results and Vik et al. (111) point out that assays have high costs that limit their feasibility in clinical practice. Osterberg et al.(15) agree stating that assays that reflect the target of medications are more costly and have limited applicability to the broad range of medications that are commonly prescribed, although the literature on adherence includes several studies that show the strengths of assays compared to other measures of adherence -particularly self-report measures. An example of this, is the study carried out by Pappadopulos et al. (46), where they looked at 254 children with Attention Deficit/Hyperactivity Disorder (ADHD) who were being treated with medication. Their aim was to examine the discrepancy between parents' verbal reports of medication adherence and a physiological measure from saliva assays. These were collected from four time points during a 14month treatment period. They found that nearly a quarter of the saliva samples

indicated non-adherence and that 25% were non-adherent 50% or more of the time. The authors concluded that the same day saliva assays suggest that nearly half of the parents were inaccurate of their child's ADHD medication adherence and that parents may overestimate adherence. Interestingly an eight year follow up of the children who took part in the study (47) found that type or intensity of treatment in the 14 months at age 7-9 does not predict outcomes 6-8 years later. Vik et al. (48) remarks that few high quality investigations have examined associations between non-adherence and subsequent health outcomes, although there is data that provides some support for increased health risks with non-adherence. However, interventions to improve adherence have seldom demonstrated positive effects on health outcomes.

It is accepted that there is no "gold standard" for measuring medication adherence, however, because medication adherence is a complex health behaviour, the authors suggest that it may be more beneficial to focus on which specific aspects of medication adherence each measure is actually measuring (49).

Pharmacy re-fill data reports on the amount of medication the patient has in their possession and not the actual medication taking itself. Self report measures are a low cost measure but have the potential for a response that has social desirability bias, although the authors suggest if this is assessed in an appropriate non-accusatory way, self report measures can help us understand the reasons for non-adherence which may identify areas for immediate intervention compared to impersonal measures such as pharmacy

claims. Medication event monitoring systems MEMS do not provide information on the actual amount of pills ingested, although studies have shown that there is at least a moderate correlation between self report and MEMS in previous research.

While recognising the limitations for each method, the most robust approach may be to use multiple measurements in order to capture a broader range of adherence information. The authors suggest that in practice in the clinical setting all healthcare providers should be at least asking patients simple questions about any problems they may be having with their medications at each visit, this may be a simple way of assessing patient's beliefs about their medicines and possible reasons for non-adherence. This however, may be a somewhat idealistic approach in the clinical area where pressures with the staff shortages and an ever increasing emphasis on measurable deliverables such as assessing a certain amount of people in a certain length of time in clinics. Most clinicians will be aware of the increase in time of a consultation if asking patients about their medications and all the perceived possible side effects they may be experiencing. Therefore it may be more appropriate and effective for patients that are non-adherent to be identified and then targeted for a multidisciplinary approach including pharmacy, psychologists, social workers, doctors and nurses.

Garber et al. (50) found in their literature search that the concordance between the different measures of adherence varies widely depending on the different measures used. Questionnaires and diaries have moderate to high concordance with other measures of adherence. Interviews and self reporting

have low concordance to electronic monitoring. They suggest that questionnaire and diary methods are preferable to interviews for self-reported medication adherence, due to patients responding in a socially desirable way or not remembering accurately when asked in interviews. It is important to remember that each measure will have its limitations and benefits with promoting adherence but only with the patient's agreement will any measure be effective and this may have to be assessed on an individual basis depending on the patient's individual circumstances and what measures are available to them in terms of finance, support and beliefs.

Kane et al. (51) point out that medication adherence is a complex multifactorial issue with factors varying between patients and changing over time. They suggest that the first step in planning interventions to improve adherence is identifying patients at risk. They acknowledge that evaluating the perceptual barriers and the role of the patient's beliefs and concerns regarding treatment provide valuable insights into the causes of non-adherence. Adherence to treatments for most medical conditions is likely to affect the outcome for the treatment, since maintaining blood levels is necessary for efficacy (52). Poor health outcomes following low adherence can in turn have an effect on the cost to society because of subsequent unresolved or worsening conditions.

Aspirin

Although prescribed to approximately 90% of persons with Cardiovascular Disease (CVD), adherence to aspirin therapy has been estimated at 70% (9, 10) (53). This may be due to the simplicity of the regimen, with typically one

tablet per day being prescribed (23). However, given that from 1998 to 2006 a two- to four-fold increase has occurred in prescribing in primary care for cardiovascular conditions, with associated cost increases (54), it is imperative that adherence to such medications be maximised to ensure value for money is achieved. Evidence suggests that reducing dosage demands is the most effective single approach to enhancing medication adherence (3).

Aspirin non-response

A further complication regarding aspirin adherence is the issue of 'aspirin non-response'. There is a growing awareness that aspirin therapy is ineffective in large numbers of patients who are prescribed the drug (55). The failure of response to aspirin whether defined in terms of platelet response, recurrent ischaemic events or using biochemical parameters has led to the concept of aspirin "resistance". There is no consensus on a definition of "aspirin resistance". Despite this lack of consensus, several studies have shown that patients, who for whatever reason are not responding to aspirin therapy, have a much higher incidence of adverse events than those that do respond to therapy.

Evidence from a previous study (12) where investigators looked at the role of enteric coating and weight on aspirin response in 244 patients with stable coronary artery disease who were prescribed aspirin, showed that approximately 19% of patients with proven cardiovascular disease attending routine clinics, have platelet function tests that are consistent with "non response" to aspirin(using serum thromboxane B2 levels). Of this 19%,

approximately half can be identified by a brief questionnaire completed by a nurse and the reason for their non-response is non-adherence with medication. However, similar to other studies that use self reported adherence measures, this is still likely to overestimate adherence (56). The exact reasons behind lack of response in the other half of patients are not clear. However, when these patients were brought back to the clinic and given aspirin and witnessed taking it, the incidence of failure to respond dropped dramatically to about 1%. Moreover, of this small amount of patients (1%) who were apparent non-responders, when they were given 150 mg of soluble aspirin they did respond, when using Light Transmission Aggregometry (11). This leads us to conclude that the lack of response is more likely to be due to non-adherence.

Assay measures of aspirin

Thromboxane A₂ is the main product of arachidonic acid metabolism through the action of cyclooxygenase (COX-1) in platelets and COX-2 in monocytes and other nucleated cells including endothelial cells where COX-2 can be expressed in the inflammatory response to stimuli. Thromboxane A₂ is a vasoconstrictor and platelet agonist with a central role in platelet aggregation and thrombosis. The inhibition of this process by low dose aspirin is estimated to give a 21-25 % risk reduction in the secondary prevention of vascular disease (57, 58). In Berger et al.'s meta-analysis (48) they found that low dose aspirin in patients with stable coronary artery disease had a 21% reduction in the risk of cardiovascular events (non-fatal MI, non-fatal stroke,

and cardiovascular death) and a 13% reduction in all-cause mortality in six studies of 9853 randomised patients.

Anti-platelet medication such as aspirin have been administered to patients at standard doses in clinical practice without monitoring their pharmacological effects by means of laboratory tests (59). Research however has revealed inter-patient response variability to aspirin and patients that display no or negligible response have been considered poor responders or resistant to treatment. Cattaneo (59) suggests that the term “resistance” to a drug should be used when a drug is unable to hit it’s pharmacological target, due to inability to reach the target due to reduced bioavailability, in vivo inactivation, negative interaction with other substances, or due to alterations of the target. Based on this definition, resistance to aspirin should be limited to situations in which aspirin is unable to inhibit Cox-1- dependent Thromboxane A2 (TxA2) production and consequently TxA2- dependent platelet functions, such as Thromboxane B2 (TxB2).

In other words, the term “aspirin resistance” should be limited to situations in which failure of the drug to hit it’s pharmacological target has been documented with specific laboratory tests (60). A review of the literature shows agreement among authors in recent years that serum Thromboxane B2 (TxB2) reflects the total capacity of platelets to synthesize Thromboxane (TxA2), and because the contribution of other blood cells to its synthesis is small, serum TxB2 is the most specific test to measure the pharmacological effect of aspirin on platelets (61-64). Suboptimal response to aspirin, as

determined by specific assay tests (serum thromboxane B2) appears to be rare and in most cases is caused by poor adherence (65).

Thromboxane B2 – Validated and Reliable measure of aspirin adherence

Over the years researchers have repeatedly found that lack of platelet inhibition from aspirin post-myocardial infarction is associated with poor health outcomes (66). Cotter et al. (210) designed a study to examine if the increase in cardiovascular adverse events were due to non-adherence or aspirin resistance. They concluded that poor outcomes were mediated by non-adherence. Several studies since have shown aspirin resistance to be only one percent and generally due to patients requiring an increase in dose or frequency due to increased body mass index or diabetes (12, 14, 67, 68). Meen et al. (68) describe their study of two hundred and eighty nine patients with stable Coronary Artery Disease where they looked for aspirin resistance with two different types of measurement for aspirin effectiveness. The first, using light transmission aggregometry and the effect of Arachadonic acid, where patients who are adequately inhibited have an aggregation response less than twenty percent. The other test is measuring serum thromboxane (using a similar assay to the current study), where the authors state the sensitivity and specificity for detecting subjects taking aspirin is ninety percent and eighty nine percent respectively. The authors advise aspirin resistance should not be diagnosed unless adherence is ensured, pointing out that many studies fail to provide adherence data, and only a few studies have witnessed aspirin ingestion (69, 70). They suggest that when in doubt, witnessed ingestion of aspirin followed by arachodonic acid induced testing is the best

method for deciding if there is true aspirin resistance or not. They conclude from their study that aspirin resistance is rare in patients with stable Coronary Artery Disease but acknowledge there are some clinical conditions that may affect patients inhibition with aspirin. They cite studies that have shown this in patients undergoing cardiac surgery (71) or carotid surgery (72), suggesting high oxidative stress may be a cause. They also suggest that it may be conceivable that patients with extreme advanced atheromatosis may have a very high turnover of platelets due to continued platelet activation on atheromatus ulcers.

Adherence or Resistance

Schwartz et al. (69) investigated the theory that aspirin resistance is often due to non-adherence. They looked at one hundred and ninety patients from a pool of three hundred and fifty patients who met the inclusion criteria of, a history of myocardial infarction and having been prescribed aspirin for greater than one month before consenting to participate. The patients were given a detailed description of the study before being invited to take part; therefore patients who tend to be non-adherent may have been deterred from taking part in the first place. Even still, from the one hundred and ninety patients, seventeen showed an ineffective response to aspirin using the standard light aggregometry and arachodonic acid. Of these seventeen patients, ten admitted being non-adherent. When these seventeen patients were administered aspirin and tested two hours post witnessed ingestion, only one patient showed lack of inhibition and then admitted to taking a non-steroidal anti-inflammatory twelve hours before testing, which is known to reduce the

effect of inhibition from aspirin (73). The authors concluded from their study that testing patients' platelet inhibition with arachadonic acid aggegometry detected a significantly larger number of non-adherent patients than verbal questioning. The authors also suggest that there was no difference in the formulations either by dose or enteric coating between those that were inhibited and those that were not adequately inhibited. They also note from their previous studies that a single dose of aspirin (either 81mgs or 325mgs) will inhibit arachodonic acid stimulation for greater than or equal to three days, suggesting the patients that were not adequately inhibited were non-adherent to aspirin for at least three days. This study is also supported by the recently published study by Grosser et al. (73) who found not a single incidence of true resistance from four hundred volunteers taking aspirin, although enteric coated doses had a lower absorption rate as expected. Patients who take their daily dose should still be adequately inhibited as shown by standard light transmission aggregometry (LTA) and serum thromboxane B2.

Schwartz et al. (69) state that previous studies showing aspirin resistance, even if associated with poor adherence, are associated with poorer outcomes and highlight the importance of assessing patients for lack of adherence. Particularly patients with multiple conditions, such as diabetes, heart failure and obesity that have previously been associated with higher resistance. Cotter et al. (210) concludes that significant adverse events and poorer outcomes due to lack of aspirin effect is mediated through non-adherence, and this contention is supported by studies that show the effect of aspirin is beneficial but not as large as one would expect. They suggest if the lack of

aspirin effect is due to non-adherence, then poorer outcomes may be due to features that are also associated with non-adherence to aspirin, not lack of effect alone. They point out that patients who are not taking their aspirin are more likely to be non-adherent to other medications, consistent with Newby et al.'s (74) previous study looking at long term adherence in secondary prevention therapies in Coronary Artery Disease, and also health recommendations including diet and exercise. They may also be more at risk of other psychosocial problems such as depression and social isolation which are also linked to increased morbidity.

Predictors of adherence

The literature on prediction of non-adherence has inconsistent findings, depending on the area being studied. Socio-demographic factors and lifestyle including alcohol intake, disease severity, and patient education and knowledge about regimen, have all been shown to predict adherence (22, 75, 76) with one study showing improvement in adherence when the education was given by nurses, but not physicians.

With the decreasing amount of time acute Cardiovascular Disease (CVD) patients spend in hospital for treatment (77), this lessens the opportunity for patient education regarding medication adherence which some studies have shown does have a positive effect on patient's adherence (12, 53). Studies assessing knowledge may fail to take into consideration the deliberate non-adherence to medications. More consistent predictors of adherence appear to be: beliefs about medicine, beliefs about illness, depression, forgetting,

prescription costs (depending on the broader health system) and social support (22, 78, 79).

Factors influencing adherence

It is estimated that there are over two hundred variables that can be linked to patient's medication adherence (33, 80). In order to make sense of this large number of factors, researchers have attempted to categorize them into groups which include personal characteristics, cognitive and interpersonal factors.

Jin et al. (81) conducted a systematic review in order to identify the most common factors that contribute to non-adherence from a patient's perspective. From patient-centred factors they considered age, ethnicity, gender, education and marital status. They found that most studies showed a positive correlation between increasing age and adherence and those studies that did not, had confounding variables such as physical disability, location, and education thus limiting generalisability of the findings. The authors argue that non-adherence in the studies on elderly patients appears more likely to be non-intentional, suggesting if the elderly are assisted by health care providers or family this can be overcome. They also suggest that middle-aged patients tend to be less adherent, due to other commitments and priorities in their daily lives, while also being less concerned about their health.

Their review found contradictory findings regarding gender and educational level, suggesting these were not good predictors of medication adherence, where education has previously been discussed this may be surprising but

they hypothesise that less educated patients may be more trusting of the physician. They did find correlations with non-adherence and ethnicity but advise that this may be due to language barriers and socio-economic status. They also found a generally positive relationship with marital status and adherence but this can be altered by disease factors. For example younger renal patients that were reliant on a spouse for their medications were less likely to be adherent whereas older married cardiovascular disease patients were more likely to be adherent. Smoking and alcohol consumption were generally related to increased lack of adherence as well as forgetfulness and lack of health literacy. The main findings from their literature search were that psychological indicators such as social support, beliefs about medicines and illness, the patient's attitude (negative or positive) and the patient-prescriber relationship were strong factors influencing adherence. They concluded that health care providers should consider therapy related problems when designing therapy plans such as accessibility, costs, frequency and complexity of treatments and the family and patient should be involved in the process of the plan for treatment in order to minimise these barriers. They suggest future studies should not only focus on demographic factors but also psychological factors.

Interventions to improve adherence

Interventions to improve adherence in CVD populations have met with modest success (23). Various strategies have been employed, which can be grouped into various themes. Of these, best current evidence suggests that prompting mechanisms and simplified dosing are likely to be beneficial, patient health

education is unlikely to be beneficial, and interventions such as prescriber education or reminder packaging are of unknown effectiveness (23). It may be surprising that patient education is ineffective; however, as outlined above, interventions have typically failed to take into account patients' own beliefs about medicines, illness or their mood states. A reminder is unlikely to prompt a patient to take aspirin if for example; they have no intention of taking the medication; they don't believe that they need aspirin; they are concerned that they may get addicted to the drug and are more concerned about the side effects (22, 82, 83). Although a substantial body of research has addressed these issues individually, the quality of the studies in this area have been criticised due to their heavy reliance on indirect measures such as pill counts and patients' self-reported compliance which Newell et al. (84) point out, is disappointing considering numerous studies and reviews have identified problems with their sensitivity and specificity for the last 20 years.

Interventions employed to improve adherence must be multifaceted, and together with practical approaches (reducing unnecessary drugs and simplifying dosage regimens), most importantly acceptable to the patient (85). Dulmen et al. (86) found in their review that there is evidence to support the simplification of dosages and packaging to improve medication adherence and the simplification of a regimen appeals to one's intuition. They also point out that initially researchers sought the reason for non-adherence in dispositional characteristics such as personality traits however there was lack of evidence to support this. They advise medical and social psychology scientists should connect with fields such as human engineering, ergonomics and technical science to explore adherence and interventions further.

Over the past few decades it has been recognised that adherence to medications is a shared responsibility between the health care professional and the patient and, in a review of the literature, the only demographic characteristic consistently associated with adherence has been age, but the direction is inconsistent depending on the population (81). It appears cognitive factors such as beliefs about illness and medications are better predictors of adherence than personal characteristics and it has been shown that patients who believe the treatment will have benefit and generally have a positive attitude regarding the treatment and illness are more likely to adhere to the prescribed regimen. Researchers such as Levesque (87) point out that social support has been shown to have a consistent influence on medication adherence (88).

We can see from the literature that overall adherence is poor (10), even with aspirin therapy which is generally only once a day. The measurement of adherence is imperfect but thromboxane B2 ELISA has previously shown to be the best objective measure available. Hundreds of factors have been shown to correlate with adherence but the following chapters will critically review what appear to be the most important ones that may have an influence on aspirin therapy in cardiovascular disease patients.

While some consideration of the magnitude of the predictive relationship between the factors outlined and the time frame for such prediction is required. There is no clear distinction between factors associated with increased adherence versus those associated with decreased adherence.

CHAPTER 2 - Beliefs about medicine

Introduction

This Chapter will outline the theoretical framework for beliefs about medicines and outline how the beliefs about medicines questionnaire (BMQ), was developed along with its psychometric properties. It will then review studies that have used the beliefs about medicines questionnaire, mainly focusing on patients with coronary artery disease and look at the different measures of adherence used.

Theoretical approaches to non-adherence, and the necessity-concerns framework

Previously, Psychology has used models such as the Theory of Planned Behaviour, the Common Sense Self-regulatory Model of Illness and the Health Belief Model, to try to explain adherence and non-adherence to medicines (52). The theory of planned behaviour can be used to predict whether a person intends to do something or not (89). Ajzen (90) suggests that this involves three things; firstly whether the person is in favour of doing it (attitude) and the beliefs about the consequences of the behaviour, secondly, how much the person feels social pressure to do it (subjective norm - how other people important to the person would like them to behave). Lastly whether the person feels in control of the action in question (how much control they have over the behaviour and how confident they feel about situational and internal factors), which Ajzen calls perceived behavioural control. We can increase the chances that the person will behave in a certain way by changing one of these predictors but the authors admit that there isn't a perfect

correlation between intention and actual behaviour and that the theory of planned behaviour is a model of human action provided that the action is intended or planned, therefore this doesn't account for non-intentional non-adherence, e.g. a patient forgetting to take their medications and the various reasons why people forget. Sniehotta et al. (91) discussed how a systematic review of 237 independent prospective tests found that the theory of planned behaviour (TPB) accounted for 19.3% variability in health behaviour with intention being the strongest predictor in longitudinal studies, but there was considerably less prediction when the studies were shortitudinal in design, participants were not university students, and the outcome measures were objective rather than using a self reported measure.

The Common Sense Regulatory Model states that illness beliefs are structured and that coping reactions depend on the way the person feels about the health threat (92) and unlike other models, considers the influence of emotional variables on health and illness behaviours. Horne et al. (16) also point out that perceived views of significant others such as family, friends and doctors may also influence patient beliefs; this model is considered in more detail in chapter 3.

The Health Beliefs Model considers variables such as perceived threat, the way the person feels they are susceptible to a condition or how severe it is; the perceived benefits of the treatment to reduce the threat of illness, and the perceived barriers, which are the negative consequences that may result from taking particular health actions. This model also considers cues to action,

events that motivate people to take action and other variables like socio-psychological or demographic that affect a person's perception and thus their behaviour. This health model like the previous two considers self efficacy, the person's belief that they can carry out the behaviour (93). However, Horne et al. (94) believed that there was a need for a psychometrically sound method for scoring commonly held beliefs about medicines in general and specific medications, as patients may have a negative belief about medicines in general but a positive belief in a medication that gives them relief from a symptom, for example analgesics.

Horne et al. (16) argued that patients' decisions about taking medications are likely to be influenced by beliefs about medicines as well as beliefs about the illness. This contention was supported by a report from the Royal Pharmaceutical Society of Great Britain (95) and Marinker (96). They pointed out that comparisons from findings from qualitative and quantitative studies previously, observing beliefs about medicines is difficult due to different questionnaires and differences in whether beliefs about medicines in general or specific beliefs are being measured. Beliefs about medicines in general are for example a belief that medicines are harmful or overprescribed, beliefs about medicines specific are patients' beliefs about a particular medicine for example their own specific medication for their own diagnosis or illness. The patient tends to then do a necessity concerns assessment of whether the benefits outweigh the risks before they decide on taking the medication. They found from reviewing the literature that a systematic comparison was difficult due to few studies using questionnaires to quantitatively assess beliefs about

medicines. A review of the literature on lay beliefs about medicines showed that there were three questions that needed to be addressed: could the nature of the beliefs ranging from general to specific be summarised into common themes which are relevant to different illnesses and different cultural groups; who holds them and how strongly are they held; and how they relate to each other with regards to specific versus general beliefs about medicines.

Research has shown that country of birth for example has an important factor on beliefs about medicines (97), those from the Nordic countries have been shown to have a more positive belief in medicines in general, also people may have a negative belief about medicines in general but a positive belief about a particular medicine for their particular ailment, as mentioned earlier.

Horne et al. (16) believed there was a need for a specific gauge to measure patient's beliefs about medicines that would inform the development of interventions to improve medication adherence. The beliefs about medicines questionnaire (BMQ) was developed as an aid to understanding people's perceptions about medicines and their adherence to prescribed regimes (17).. As shown from the previously mentioned research and theories (82, 83, 98), the cognitive processes are simply more complicated. Decisions are likely to be informed not only by beliefs about medicines but also beliefs about illness which will be described in the next chapter.

Development of the BMQ (Beliefs about Medicines Questionnaire)

The BMQ was therefore developed to address this theoretical gap in the literature with the aim to assess the broad range of common beliefs about

medicines that people hold from a pool of 34 statements (94). This pool of statements was generated from the previous literature which appeared to be common to patients with a range of chronic illnesses and from interviews that they conducted with 35 patients - 20 haemodialysis patients and 15 patients post myocardial infarction that were chronic and currently prescribed regular medication. The interviews were carried out using open ended questions in order to identify beliefs that had not emerged in previous research.

General and specific - beliefs about medicines

The “beliefs about medicines questionnaire” contains two sections, the BMQ specific and BMQ general. The questions were developed from interviews with chronically ill patients. A chronic illness sample of 524 patients of asthmatic, diabetic and psychiatric patients from hospital clinics and cardiac, general medical and renal in-patients were invited to take part in a study of patients’ views about their illness and treatment. The patients were reassured that the researcher was independent of the hospital and the responses were confidential and would not be seen by any of the staff involved in their care. This was with the aim of avoiding response bias, which is known to happen when the researcher is associated with the clinical team.

The cardiac sample of 120 in-patients was chosen for the initial analysis of the beliefs about medicines specific questionnaire, as it was the largest diagnostic group within the main sample. The rationale for choosing a single group was that patients with one illness might receive very different medication from those with another diagnosis, e.g. psychiatric patients. The primary aim was to simplify the fairly broad range of beliefs into core themes, which could then

be analysed. This was done from a 34 statement pool of commonly held beliefs about specific and general medication identified in the literature and from interviews with 35 chronically ill patients (haemodialysis and post myocardial patients), as mentioned earlier. Twelve items were positive and 22 were negative or neutral statements about medicines. The aim was to explore beliefs about medicines as a broad concept rather than beliefs that might be unique to a particular illness. The rationale for limiting initial factor analysis in the specific beliefs about illness groups did not apply to the general group, as the aim was to explore medication beliefs as a broad concept (16). Data were combined from asthmatic, diabetic and renal patients to investigate themes which would be common across chronic illness populations. Principle component analysis showed an 18-item, 4-factor structure which was stable across six illness groups – asthmatic, diabetic, renal, psychiatric and general medical (17). The BMQ *specific* subscale consists of two 5 item factors assessing beliefs about the need for the prescribed medication and concerns that an individual is prescribed for a particular illness (-see Appendix B). The BMQ *general* consists of two 4 item factors assessing beliefs that medicines are harmful, addictive, poisons which doctors over-prescribe, and that perhaps should not be taken continuously, this is their beliefs in general and not necessarily about those that are prescribed (16) (Appendix B).

In summary, the four item factors for general and specific beliefs about medicines are concerns, necessity, harm and overuse. It was hypothesised that the stronger the beliefs in the necessity of prescribed medications the higher the reported adherence. It was also hypothesised that people who

believe medicines to be harmful or overused in general by doctors may be more inclined to seek alternative treatment. The 8-item BMQ general questionnaire was administered to the pharmacy clients and the alternative therapy group to see if there were differences between the two groups. The BMQ scales were able to distinguish between patients in different disease groups as predicted. The diabetic patients had a higher specific necessity score while the asthmatic and psychiatric patients had higher specific concerns scores. The alternative therapy group had higher concerns about medications than the pharmacy group as predicted.

Psychometric properties of the BMQ

Psychometric evaluation was carried out from the results of the above and the BMQ was then administered to participants from a community pharmacy and participants who were attending complimentary care.

A matched group of 72 patients attending a community pharmacy and a complementary therapist (homeopathic/herbal clinic) were recruited to compare medication beliefs between the two groups. There were no significant differences between the two groups in terms of age and gender. There was a significant difference in educational experience with the group attending the alternative therapists in that it was higher than the group attending the pharmacy for conventional medication; this has been shown in similar studies (98) where people attending alternative therapists had on average more years of formal education than the typical person. This group also made more visits to their homeopath in the previous 6 months before the study although there were no differences in attendance to the general

practitioner or hospital admissions. Thus both samples were considered comparable in terms of illness severity. The hypothesis here was that the homeopathic group would have higher scores than the pharmacy group, when asked questions regarding general harm of medicines and overuse and over prescription (16). Results showed patients attending complementary therapy had significantly higher scores on the general harm ($P < 0.05$) and overuse ($P < 0.001$) scores than those presenting to the community pharmacy.

The authors report that the internal consistency of the general harm sub-scale was disappointing in the asthmatic, cardiac and general medical groups but a greater degree of consistency was found with the other data sets. (16).

Examination of the data showed that this was not due to a single outlier item but a true reflection of low internal consistency, and they suggest that this may be due to certain illnesses producing different beliefs about medicines depending on past experiences with prescribed medications. Despite this, they state that the discriminant reliability and validity of the BMQ support its use in research.

Furthermore, beliefs about medicine appear to be stable over time. The findings from the study by Porteous et al. (52) to compare beliefs about medicines over time where they looked at the BMQ general given to the same people between 2002 and 2005. They found that general beliefs about medicines appear to remain stable over time, irrespective of changes in health status. The authors suggest that the observed stability in general beliefs about medicines is consistent with previous research that showed that health beliefs

are stable from a young age, therefore, further supporting the theoretical construct as it is stable over time (99).

Intentional and non-intentional adherers

Clifford et al. (100) found in their study of patients that were newly started on medication for a chronic disease, that patients who did not adhere to their medication intentionally had lower perceptions of the need for the medication compared to adherers and more concerns, unintentional non-adherers were not significantly different from adherers. This may be due to the reasons outlined above, that socio-psychological, perceived behavioural control and emotional factors such as stress may have an effect on non-intentional adherence. Intentional non-adherers were more likely to rate their concerns as high relative to their need for treatment compared to both adherers and unintentional non-adherers (101). In this study they found that patients with strong concern beliefs in medicines were more likely to report an adverse drug event while controlling for confounding variables such as socio-demographic, clinical and behavioural factors. The authors suggest that these patients may be more sensitive and pay particular attention to unwanted reactions possibly making them more likely to report an adverse effect. Socio-psychological variables such as concerns in beliefs about medicines may be more important than the number of medications, (which the researchers state was not significant in any of the studies) in the self reporting of adverse drug events, because symptom cause and relatedness to medicines may be based on the patients motivation to tolerate the adverse effects or the patient's past experience with using the medicine.

Overall, this research shows the patient's belief about medicines appears to be an important variable associated with adherence, symptom reporting and adverse drug events (102) .

Beliefs about medicines in patients with Coronary Heart Disease (CHD)

The following section reviews literature published from 2000 onwards that has assessed the Beliefs about Medicines Questionnaire (BMQ) and adherence in CHD patients. Table 1 provides an overview of these 12 studies.

TABLE 1- Beliefs about medicines a review of the literature

Author,year,country	Sample setting	Study design	Sample Size	BMQ, adherence and other measures	Results	Comments
Allen LaPointe 2011 USA	ACS pts from 41 hospitals	Prospective study with telephone follow up 3mths post ACS	973 pts	BMQ-specific	Non-adherence 23-26% In adjusted analysis greater perceived necessity for heart medications was significantly associated with lower non-adherence. B-blocker OR-0.94,95%CI 0.91-0.98-23% non-adherence. ACE/ARB-OR-0.94,95%CI 0.90-0.98-26% non-adherence. LL-OR1.09,95%CI 1.05-1.14 non-adherence23%.	Self report measure of adherence-known to overestimate adherence but higher adherence was found in cardiac rehabilitation patients and younger age was significant with non-adherence.
Bermingham et al. 2011 Ireland	Cohort of pts from the STOP Heart failure study- primary care clinics-2 even groups of achievers of LDL-C and non-achievers	Prospective longitudinal RCT study-randomised selective subgroup.	185 pts	General BMQ LDL-C MMAS-Morisky Medication Adherence Scale	48% reported not fully adherent, 25% non-adherent intentionally. BMQ significant predictor P- .036 adjusted of self report adherence but not LDL-C goal achievement.	Only 17.5% had CAD, only 45% male (not representative of other CAD samples). Only 65% answered the call and completed questionnaire. Only 34% goal achievers. MMAS not BMQ-G was predictive of LDL-C goal Self report-not objective
Byrne et al., 2005 Ireland	Established CHD from 35 GP practices , 1577 pts sent questionnaire,1084	Observational, cross sectional	1611 Charts 1084pts From 35 G.P practices	IPQ-R,MARS-5 BMQ Specific and General	Medication beliefs only moderately related to self reported non-adherence, explaining 7% of the variance,	Good response rate from questionnaires no significant correlation. Pts >80yrs were excluded. illness

	returned					perception only weak predictor perhaps due to low symptoms and threat
Calvert 2012 USA	Documented CAD pts from x2 hospitals	RCT cross sectional postal survey 6mths follow up	143 pts	BMQ specific MAS and pharmacy refill records.	No sig. difference between Control and intervention groups. BMQ did not predict adherence.	24% didn't complete follow up. Self report – accuracy although 71% of pts reported long term adherence to aspirin . Level of agreement between both measures (MAS and refill) was poor for adherence but shows the need for more robust measures in practice.
Clifford et al. 2008 UK	Community pharmacy pts collecting a new medication for a chronic condition with an inclusion criteria of one of the following- >=75yrs or older History of- Stroke- CAD-Asthma- Diabetes or Rheumatoid arthritis.	Longitudinal cross sectional survey.	258 pts Consented 93% took part in telephone interview, 705 returned questionnaire	BMQ-specific	70% adherence 30% non-adherence (if they missed a dose in the last week). There were sig. differences in beliefs between adherent and intentionally non-adherent pts having more concerns and less perceived need P=0.2	Doesn't measure unintentional non-adherence as its self report over the telephone (no. of non-adherence was too small for subgroup analysis at 4mths)
Horne et al. 2010 UK and Scandanavia	A subset from the ASCOT study that	RCT comparing 2 pharmaceutical	230 pts from the ASCOT	BMQ specific Beliefs about	40% were adherent 45% complete adherence.	Self report and tablet count

	were't recruited for a comparison group.	approaches to hypertensive management.	study-106 for the comparison group.	illness	Significant correlation with concerns on BMQ P<0.001	
Khanderia et al. USA (2008)	Coronary Artery Bypass pts surveyed at 6-24mths after surgery	Cross sectional	132 completed questionnaire from 387 surveyed	BMQ-specific and general 4 item MAS	55% were adherent by self report, non-adherent pts were in stronger agreement in general overuse-P=0.01 and general harm-P=0.04	Only 34% completed questionnaire and an objective measure was not used.
Mardby et al.((2007) Swedish	Pharmacy clients, who were mainly on cardiovascular medications.	Observational-cross sectional	324	BMQ-General MARS	54% were non-adherent An association was found between general harm and adherence (Odds ratio) OR=0.46,CI=0.30-0.70	Country of birth was found to be an important factor for beliefs about medicines, those from the Nordic countries believed medicines to be more beneficial
Muntner et al. 2011 USA	Post PCI pts before discharge from hospital	Prospective	284 pts	BMQ Morisky self report scale, MMAS self report	11% low adherence to clopidogrel OR 6.13 CI(1.34-28.2)	Similar results to our study with regards to males and females and self reported non-adherence to anti-platelet medication
Sjolander(2013)	Stroke pts who have cardiovascular disease and prescribed anti-platelet therapy-3mths after	A cross sectional questionnaire survey	989	BMQ-General and specific. MARS	12% non-adherent-scored lower on positive beliefs about medicines OR=0.90,95%CI 0.83-0.98	Only a minority of pts responded non-adherent, statistically significant-possibly different type of pts
Sud et al. 2005 USA	ACS pts	Cross sectional Interviewed 10mths after discharge	208	BMQ –specific and general 4 item MAS	87.4% adherence to Aspirin-final regression model showed R(2)=0.132 and included health related status and specific necessity P=0.02 as predictive	Self report of 87.4 % adherence to Aspirin is probably an over estimate- not objective.

					variables that were significant.	
Van der Wal(2006) Netherlands	Heart failure pts	Descriptive cross sectional	501 HF pts	BMQ- appears to be general but not clear. Revised HF compliance scale CES-D centre for Epidemiology survey depression scale Compliant 5 point likert scale Dutch HF knowledge scale	72% compliant 98% compliant with medication Beliefs about medicines in general OR=1.78;C.I 1.18-2.69-associated with better adherence. Compliant patients had less depressive symptoms OR=0.53 C.I 0.35-0.78	The self report of 1.4 % non-compliance is unusually low

ACS=Acute Coronary Syndrome, BMQ=Beliefs about Medicines questionnaire, B-blocker=Beta blocker, ACE=Angiotensin Converting Enzyme,

ARB=Angiotensin receptor blocker, LL=Lipid Lowering medications, LDL=Low-Density Lipoprotein, CHD=Coronary Heart Disease, CAD=Coronary Artery

Disease, RCT=Randomised Controlled Trial, MAS=Medication Adherence Scale, MMAS=Morisky Medication Adherence Scale, ASCOT=Anglo-Scandinavian

Cardiac Outcomes Trial, PCI=Percutaneous Coronary Intervention

Overall, the studies in Table 1 show the following important finding. Firstly, medicine beliefs appear predictive of adherence, with 9/12 studies demonstrating this (97, 100, 103-109). However, the studies also show a number of limitations: only two studies used objective measures of cholesterol level (104) and blood pressure reduction (103) which may also be affected by diet and exercise. Therefore, a study which assesses aspirin adherence using the best objective measure could be a real addition to the literature, as the effect of diet and exercise do not affect the inhibition of thromboxane B₂ by aspirin (12). The fact that there are few studies that have used an objective measure is a major limitation. As Allen Lepoint state (103) in 2011, that the application of the beliefs about medicines questionnaire within clinical practice is untested and additional research is needed in translating this or similar instruments into clinical practice to assess their feasibility and outcomes. The authors at this time suggested that this was the first evaluation of the BMQ specific in patients with ischaemic heart disease.

Horne et al. (2) have demonstrated that beliefs about medicine were more powerful predictors of self-reported adherence than the clinical and socio-demographic factors in patients with heart disease. Gender, education, or the number of prescribed medicines, did not predict reported adherence (2). A recent study in a similar cohort of patients with Cardiovascular Disease (CVD) looking at adherence to cholesterol control medication found that 25% of patients who reported non-adherence were intentionally doing so. Patients' beliefs about medicines were a significant predictor of self-reported adherence but not of the cholesterol goal achievement (104). This may be

due to the measure of adherence which was self-reported and previously shown to consistently under estimate non-adherence. This may also be due to other confounding variables such as exercise and diet changes in behaviour, which are known to have an effect on cholesterol levels. This was shown in a recent study by Ho et al. (110) where in a randomised controlled trial using a multifaceted approach intervention to increase adherence of cardiac medications found an increase in medication adherence in the intervention group, but not in the outcomes of blood pressure reduction or cholesterol level or major adverse cardiac events (MACE). The authors admit the limitations of this study were the measure of adherence, which was pharmacy refill data which doesn't prove ingestion and the study should have continued past twelve months when adherence was likely to reduce significantly.

The recent similar study(to the proposed study) carried out by O'Carroll et al. (13) found a relationship between beliefs about medicines and adherence to aspirin therapy but were not able to use their objective measure as it was deemed an unreliable measure, as mentioned above. This was due to measuring thromboxane level in the urine as an indicator of adherence but during the study the investigators found that the measure was unreliable as it was unable to differentiate between those that were on aspirin therapy and those that were not.

Horne et al. (111) have recently completed a meta-analysis of studies that have used the BMQ to assess patients beliefs about medicines in long term conditions including some with Acute Coronary Syndrome (ACS) but most use a self-assessment method of measuring adherence. They also fail to point out

the major limitation of the O'Carroll (13) study which used an objective measure of aspirin in the urine but the measure was found to be inaccurate therefore not a valid measure of adherence.

BMQ used in Coronary Heart Disease - specifically

Byrne et al. (112) study looked at the charts of 1611 established coronary heart disease patients and was designed to evaluate the use of illness perception and medication beliefs in predicting secondary preventative behaviour among patients with coronary heart disease. They found that an illness perception approach did not predict secondary preventative behaviour among this group of patients, while beliefs about medicines appeared to be a reasonable predictor of medication adherence, although the measurement used was a self reported measure. The authors also suggest that their study reinforces the need for a holistic approach in designing interventions to increase secondary prevention of heart disease, agreeing with previous research that attendance at cardiac rehabilitation clinics is more likely in patients who perceive their illness as controllable, serious and caused by lifestyle factors (113, 114). Byrne et al. (70) suggest that findings from their study again emphasize that lifestyles are complex and influenced by many factors.

Birmingham et al.'s (104) prospective study of LDL-C goal achievement and self reported medication adherence among statin users in primary care, used the beliefs about medicines questionnaire and the Morisky Medication Adherence Scale to observe for relationships. They found that 25% of patients who were non-adherent were non-adherent intentionally and beliefs about

medicines were a significant predictor of self-reported adherence but not of LDL achievement.

Bane et al. (115) also used the beliefs about medicines questionnaire in their study looking at the impact of depressive symptoms and psychosocial factors on medication adherence in cardiovascular disease in 122 patients attending a cardiac clinic. They found 14.8 % of patients were non-adherent using a self report and 41.7% had scores of depressive symptoms measured by the centre for Epidemiological studies Depression Scale. They found that high scores on the depression scale and high scores on the concern scale of the BMQ were found to be associated with self- reported non-adherence. Again one of the limitations of this study is that non-adherence is self-reported which may underestimate non-adherence.

Self Report Adherence in Cardiovascular studies

A recent example of self reported adherence used in cardiovascular disease (CVD) patients is the UMPIRE study (116), where the effects of the “polypill” with a fixed dose combination of drugs for blood pressure, cholesterol, and platelet control were compared to usual care resulted in significantly improved medication adherence at 15 months and statistically significant but small improvements in systolic blood pressure and cholesterol LDL- C.

The fact that this study used self report for medication adherence could be the reason for only a small improvement in blood pressure and cholesterol level.

Rinfret et al.’s study (117) looking at the effects of telephone contact to improve adherence to dual anti-platelet therapy after drug-eluting stent implantation, also used self report and pharmacy refill to assess medication adherence.

They found that in 300 patients randomised to two groups with the intervention group receiving four phone calls in 1 year, adherence was 99 % in the intervention group and 90 % in the control group. The obvious limitation with this study is the non-objective direct measures used to measure adherence and the fact that adherence was so high in both groups compared to adherence in other studies, including clinical trials where the patients are monitored and reminded on a more regular basis and adherence of 90% would be considered high and unlikely.

Kripilani et al.'s (118) study of age, health literacy and medication management strategies with cardiovascular medication adherence found that age less than 65 years and marginal or inadequate health literacy, were independently associated with medication non-adherence using refill and self reported adherence but they also found that medication strategies did not explain these relationships.

A meta-analysis by Demonceau et al. (119) with the aim of identifying and assessing adherence enhancing interventions through electronically compiled dosing histories, found that their analysis was limited due to the heterogeneity and disparities in the data and the different measures of adherence. The authors suggest the limitations of their analysis highlight the urgent need for defined guidelines for research protocols that will guide researchers in designing studies to accurately assess the effects of adherence- enhancing interventions.

Conclusion

Overall from this Chapter, we can see that there has been a large amount of research on the beliefs about medicines and the theoretical approaches that support it make good “common sense” but self-regularity behaviour is very individual with many influences. What makes good common sense to one person may not seem like good common sense to another person i.e., not taking one’s prescribed aspirin when you have a history of coronary artery disease .If a patient looks up contra-indications to aspirin they will be advised not to take it with alcohol, therefore it may make sense to an individual not to take aspirin when they are on holidays and taking alcohol. There are many studies that have used the beliefs about medicines questionnaire but none that have used it with a reliable objective measure of adherence in Coronary Artery Disease patients. The next chapter discusses how illness perceptions also has an influence on adherence and how the beliefs about illness and beliefs about medications are linked.

CHAPTER 3 - Illness Perceptions

Introduction

As described in the previous chapter, the social cognitive models, the health belief model (HBM), the theory of planned behaviour (TPB) and the necessity-concerns framework have been used to describe adherence and non-adherence in patients. This chapter concentrates on the self-regulation model by Leventhal, where the decision to take the prescribed medication makes “common sense” to the patient, in light of their experience and how this may be influenced by past or current symptoms, or the views of significant others (120). The chapter will also describe the development and psychometric properties of the illness perception questionnaire and show the studies that have used illness perceptions in relation to adherence, mainly concentrating on studies with patients with coronary heart disease.

Self-regulatory model

Leventhal’s self-regulatory model of illness (SRM) has been used in the study of medication adherence whereby the decision to take prescribed medication or not, is conceptualised as a coping response to a perceived health threat (120). Leventhal’s theory is a system of conscious personal health management where self-regulation includes impulse control and the control of short term desires; the theory implies that people with low impulse control are prone to acting on immediate desires. When this is related to health behaviours, a patient will only take a doctor’s advice with a certain amount of self-regulation, and for medical treatment to be effective, the patient needs to be interested in improving their own health. The patient will then evaluate their

own behaviour and the effect this is having on their health, altering their behaviour to achieve the desired effect (121). Self-regulation has been described by authors (122) in relation to humans controlling their thoughts feelings and desires in anticipation of higher goals. The authors point out that most studies have concentrated on self-control failure which may be due to the large amount of people that fail to act out their intentions or stick to their goals after their initial attempts to change their behaviour. Some theories suggest that people try harder to attain their goals when they are confronted with difficulties but these authors have questioned this theory with the argument of how people with a particular health goal i.e. giving up smoking, will give up easily if they don't see an immediate positive result or perceive obstacles (101).

Leventhal's theory of self-regulation model is one of the few models that looks at coping (123). The model suggests that mental representations of actual or future health threats are ways that patients deal with the health threat. Research suggests that patients develop their ideas about illness around different components which consists mainly of; identity – which labels the illness and which the patient relates to symptoms, cause – what the patient thinks may have precipitated the disease, and timeline – how long the illness will last. Adherence is more likely if the patient perceives the advice to take the medication prescribed makes common sense to them in light of their past experiences and may be related to symptoms and their beliefs about their illness. This theory proposes that the patient is guided by beliefs about the nature, duration, causes, consequences and potential for cure or control of

the illness (70). Regarding causal attributions, higher use of primary healthcare facilities has been associated with psychological stress and lifestyle attributions for all patients, whereas accident or chance attributions were associated with higher use for patients with a chronic disorder but lower use for patients without a chronic disorder. In general causal attributions have been less successful in predicting health outcomes than the other illness perceptions (124). Psychological and lifestyle attributions have been shown to be significantly associated with previous and succeeding healthcare use. The literature suggests that attributing symptoms to stress may be an expression of transient strain, whereas psychological and lifestyle attributions may reflect dispositional patterns of reacting i.e. smoking, alcohol and bad diet. The decision to take medication or not is likely to be informed by beliefs about illness as well as beliefs about medicines, and this has been recognised by the Royal Pharmaceutical Society of Great Britain 1997 with other researchers (82, 96). Horne et al. (82) believed there was a need for a psychologically sound method for measuring these beliefs in order to understand common themes with illness groups and cultures while understanding how they relate to other beliefs such as beliefs about medicines as well as adherence behaviour.

Development and Psychometric properties of the illness perception questionnaire

Researchers since the 1960's have studied illness representations mainly using open ended interviews, but as knowledge has developed and Leventhal's self-regulatory model has been more widely used, more objective measures were developed (125).

The illness perception questionnaire (IPQ) was administered at the same time as the Beliefs about Medicines questionnaire in order to measure its constructs by Horne, Weinman and Hankins as described above (17). The psychometric properties were previously evaluated by Weinman et al. (94) in seven different disease groups of patients including patients with diabetes, rheumatoid arthritis, asthma, chronic fatigue syndrome, chronic pain, recent myocardial infarction, and renal patients, thus the patients were a combination of chronic and acute conditions. Data from myocardial and renal patients showed good levels of both internal consistency and test-retest reliability. The authors expected this as control cure and consequences have higher levels of test-retest reliability than identity and timeline as patients' perceptions of the cure and consequences of their illness are less likely to change over time. Patients with a stronger illness identity are more likely to perceive more serious consequences from their illness with less likelihood of a cure or control over it (65).

A revised version of the illness perception questionnaire (IPQ) scale, the IPQ-R added more items to the questionnaire looking at control dimensions of personal control and treatment control while exploring emotional aspects more. The IPQ-R has over eighty items and therefore has been recognised as not a practical tool in the clinical setting, in particular for elderly or acutely ill patients or when the researcher is measuring several constructs, as this can be a large burden not only on the researcher but more importantly the patient (100). The IPQ-R has been found to be beneficial to researchers who are

mainly looking at specific symptoms and associated illness perceptions and in particular provides more information on cyclical timelines (100).

Broadbent et al. (100) saw the need for a shorter questionnaire- the BIPQ (Brief Illness Perception Questionnaire) that would be more practical in the clinical setting using a 9 item questionnaire that summarised the content in each subscale of the IPQ-R, with a scale of one to ten rather than the Likert scale. The first five items on the BIPQ questionnaire assesses illness representations, while question six and eight assess emotions (see Appendix B). Question seven assesses illness understanding. The last item, number nine assesses the three most important factors that the patient perceives as the cause of their illness, which can be grouped into categories for analysis. The psychometric properties were then assessed in different disease groups of patients with a diagnosis of Myocardial Infarction, renal disease, type 2 diabetes, asthma, and a group with minor illnesses such as an allergy or a cold. There was also a group of patients undergoing stress tests that were having angina symptoms.

The test re-test reliability of the BIPQ was assessed in renal patients attending out-patient clinics at baseline, three weeks, and six weeks, this showed good reliability over the different time periods. The construct validity of the questionnaire was assessed in the renal, diabetic and asthma sample that completed the IPQ-R and the BIPQ, this showed the equivalent scales to correlate appropriately although correlations between personal control and treatment control were low. Broadbent et al. (100) point out that previous

research has found higher perceived control and self-efficacy to be related to better self reported adherence to diet, medication and exercise, although the research appears to be conflicting when looking at glucose monitoring levels in the diabetic patients, possibly due to the disparities between self reported adherence and actual behaviour as described by Sniehotta (91).

The predictive validity of the BIPQ has been shown in patients following myocardial infarction, where a multivariate analysis of variance found that patients who attended rehabilitation classes had a higher identity score measured at hospital discharge than those patients that did not attend cardiac rehabilitation. They also found that patients with higher scores on the concern scale and treatment control beliefs were significantly slower to return to work (126). The BIPQ at discharge also predicted anxiety and quality of life.

Discriminant Validity

To assess the discriminant validity and the extent the BIPQ questionnaire could distinguish between different illnesses, the mean scores were compared between the illness groups, which the authors point out differ in clinical presentation and symptoms. As hypothesised, the personal and treatment control beliefs were highest in the post myocardial infarction patients who would have been the most acute of the groups and therefore receiving new treatments and lifestyle advice at a time when they are likely to feel medication has saved their life and relieved acute symptoms. Patients with the lowest personal and treatment control scores were as expected, the patients with the minor illnesses such as colds and allergies who may feel that they have a virus and that medication may not relieve symptoms for, for example antibiotics. This group of patients tended to report the highest

identity, lowest understanding, shortest timeline and highest emotional response, which the authors suggest is a fear response to an unknown diagnosis and effective treatment. The authors point out that while there were differences in sampling methods between patient populations, some were sent the questionnaire by post and some were recruited in the clinical area, this is unlikely to have caused a major effect on patient's perceptions (106).

Illness perceptions and adherence

Petrie et al. (126) suggest from their study of an early intervention in changing perceptions after a myocardial infarction that if negative thinking about a myocardial infarction can be identified early while the patient is in hospital, this may improve illness perceptions and levels of functioning and therefore promote an earlier return to work. Patients are often reluctant to discuss their beliefs about their illness in medical consultation because they fear being seen as stupid or misinformed (125). Fischer et al. (127) concluded in their studies that coping with an illness is a continuous process and the achievement of desired outcomes during treatment is likely to enable patients to adopt a more positive representation of their illness.

Illness perceptions have not only been linked to self-reported adherence (22, 82), but also to more objective measures of adherence (79). In the study by Molloy et al. (61), beliefs about heart failure appeared to be associated with objectively measured adherence to ace inhibitors by measuring serum levels of angiotensin-converting enzymes. They found that 72% were non adherent using this as an objective measure, and 19% of this variance was associated

with beliefs about illness. In this study of patients with heart failure, patients who believed that their illness had a longer-term duration, and had beliefs about greater consequences of heart failure on their lives, were less likely to adhere to medication. These patients had a diagnosis of heart failure, which is a condition that is typically chronic in nature, with a high percentage of patients with psychological contributing factors such as depression (128), therefore it is unclear whether these beliefs would survive adjustment for depression.

Brandes and Mullen (129) recently completed a meta-analysis to explore whether mental representations derived from the common sense model were able to predict adherence in chronically ill patients. Twenty eight out of thirty studies used a cross sectional design and adherence to medication was assessed in twenty six studies with none using an objective measure of adherence, making it difficult to make causal relationships.

Aalto et al. (130) point out that very little work has systematically explored illness perceptions in homogenous or specific illness groups and the self-regulatory theory has found many factors that influence illness perceptions but has not defined ways in which these influences occur. They explain the importance of understanding how illness perceptions are developed and how they may be modified and to which type of patients interventions should be tailored towards. Interestingly they found that older patients perceived fewer symptoms of Coronary Heart Disease and shorter expected timeline. It could be argued that the older patients may have developed effective coping skills and self-efficacy than the younger patients. They also found that illness

perceptions were related to both personal and social resources, in particular patients with strong perceived self-competence or self-efficacy, perceived less CHD-related symptoms, felt more control and perceived less consequences of their Coronary Heart Disease. They explain that those who feel more control and competence over their life may use more effective coping strategies to deal with the challenges of a chronic disease. Although the authors did not measure adherence in this study, their theories do have implications on medication adherence suggesting that if we modify patients' perceptions on self efficacy and resource support this may have a positive effect on medication and behavioural adherence.

Illness Perceptions and Coronary Heart Disease.

The literature on patient education appears conflicting and has not always shown to be effective, although education specifically targeting patients' beliefs about illness have shown some promise in improving outcomes. These studies have consisted of exploration and clarification of illness beliefs. A previous randomised trial showed that such a brief psycho-educational hospital intervention designed to alter cardiac patients' illness perceptions succeeded in improving functional outcomes post-MI (131). Those who received tailored education/clarification depending on their illness perceptions reported they were better prepared for leaving hospital, returned to work at a significantly faster rate, and reported significantly lower rates of angina symptoms and control. Such an intervention could theoretically be augmented by also including clarification about medicines (132), which is hypothesised to extend and improve the predictive ability of the illness perceptions models (22, 82, 83). As little research has to date assessed such beliefs alongside

objective measures of aspirin adherence, it is difficult to calculate the numbers of participants who could be targeted in subsequent intervention.

Studies that assess illness perceptions and adherence in patients with CHD are outlined in Table 2.

TABLE 2- Illness perceptions and adherence in patients with CHD- A review of the studies.

Author,year, country	Sample setting	Study design	Sample Size	Illness perception questionnaire and other measures	Results	Comments
Byrne et al., 2005 Ireland	Established CHD from 35 GP practices , 1577 pts sent questionnaire,1084 returned	Observational, cross sectional	1611 Charts 1084pts From 35 G.P practices	IPQ-R,MARS-5 BMQ Specific and General. Extended version of illness perception questionnaire.	Medication beliefs only moderately related to self reported non-adherence, explaining 7% of the variance, illness perception only weak predictor perhaps due to low symptoms and threat	Good response rate from questionnaires no significant correlation. Pts >80yrs were excluded.
Senior and Marteau (2004) UK	Patients with Familial Hypercholesterolemia	Descriptive study using questionnaire	336 patients	MARS 5, Anxiety, Depression, IPQ	Overall pts reported high levels of adherence although 63% reported some level of non-adherence. History of CHD, no formal qualification and perceiving genes to be important determinants of heart attack were significant from the IPQ-causal effect.	Self report measure- no participant reported poor adherence. The 63% reporting some level of non-adherence are likely to be under estimating their non-adherence
Senior and Marteau (2007) UK	CVD patients	Cross sectional questionnaire at 1 week and 6 months	317 patients	IPQ-R, MARS, behaviour.	Perceiving medication as an effective strategy for risk reduction was associated with being totally adherent OR=1.94 but didn't predict	Only 50% of this sample had coronary heart disease.

					adherence longitudinally. Effects of illness perception very small	
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CHD=Coronary heart Disease, IPQ-R=Illness Perception Questionnaire Revised, IPQ=Illness Perception Questionnaire, MARS=Medication Adherence

Rating scale 5, BMQ=Beliefs about Medicines Questionnaire, PHQ-9=Patient Health Questionnaire 9.

There are few studies that have looked at illness perceptions in Coronary Heart Disease (CHD) and even fewer that have measured adherence with objective measures. Only two studies are shown in Brandes and Mullen's (111) meta-analysis from patients with Coronary Artery Disease looking at the correlation with medication adherence and neither of these studies used an objective measure of adherence. The study by Senior and Marteau (133) is included in the table above as some of these patients would have coronary artery disease also. Brandes and Mullen (129) advise that future studies need to consider the use of other theories and must pay particular attention to the measure of adherence behaviour as their literature shows only one objective measure out of the thirty studies that they reviewed.

Byrne et al. (112) designed their study to evaluate the degree to which variations in secondary preventative behaviour, including medication adherence, could be explained by illness perceptions and beliefs about medicines in patients with established Coronary Heart Disease. Previous research in patients with asthma had shown these two measures to be predictive of non-adherence to preventative medication. They found that older patients and medical card holder patients (for whom medications cost less) reported higher medication adherence and only a longer expected timeline was a significant illness predictor of medication adherence. They found that the stronger the perception that the illness was chronic, the higher the medication adherence. This appears conflicting to the literature, as most studies have shown the more chronic the disease the more non-adherence, although this may be due to differences in perceptions of different disease

groups. Patients with heart failure for example would be more chronic in nature than patients with chronic coronary artery disease. The authors concluded from their study that an illness perception approach did not prove helpful in predicting secondary preventive behaviour, including medication adherence. The only illness perception dimensions that proved independently predictive of behaviours were found to be emotional representations which possibly links to the correlations found with depression (see next chapter); a stronger belief that one's own behaviour was a cause of the illness was related to higher consumption of alcohol. Their findings were conflicting regarding the findings between emotional representations and health related behaviours, lower levels of emotional representations were related to more exercise activity. Finally, the medication adherence in this study again was self reported and particularly high which the authors acknowledge is a limitation due to conducting such a large scale study with a postal survey.

Conclusion

The literature on the theories that underpin social cognition models (SCM), such as the health belief model (HBM) and the theory of planned behaviour (TPB) have recently come under scrutiny and criticism (91, 134) suggesting that they are only predictive of affluent young people when they are self reporting in the short term i.e. university students. They propose that psychological theories should define their range of applications rather than claiming that they can explain all human behaviour. Despite these criticisms researchers such as Broadbent, Weinman and Horne (22, 94, 135) believe

that Leventhal's self-regulation model (136) can be used as a good indicator of whether a patient will decide to take their medication or not if it makes common sense to take the prescribed medication based on their beliefs. Broadbent has shown good reliability and validity of the brief illness perception questionnaire (BIPQ) and it has been used in several studies across a wide range of illnesses as shown by Brandes and Mullen's meta-analysis (129). Unfortunately there are only two examples of illness perceptions used in coronary artery disease in their meta-analysis, with neither of them using the BIPQ and both using a self report measure. Therefore the use of an objective measure of aspirin adherence would fill a significant gap in the literature.

CHAPTER 4-Depression

This chapter will describe depression and its outcomes and its relationship with adherence. It will then explain the patient health questionnaire, its psychometric properties and its development into the brief patient health questionnaire. Finally, it will show the research that explores the relationship between depression and adherence to medications in patients with cardiovascular disease.

As mentioned in the previous chapter, emotional factors may also be important for adherence. Depression is one such factor. Depression is a common mental disorder characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration (43). It can be long lasting or recurrent, impairing a person's ability to function at work or school, or cope with daily life. At its most severe, depression can lead to suicide. When the depression is mild, depression can be treated without medicines but, when moderate or severe, people may need medication and professional talking treatments. Non-specialists can reliably diagnose and treat depression as part of primary health care. Specialist care is needed for a small proportion of people with complicated depression or those who do not respond to first-line treatments (137).

Depression is associated with several unhealthy behaviours including smoking, physical inactivity and medication non-adherence (138, 139).

Patients with depression have many risk factors that can contribute to non-adherence to their medications including changes in cognition and

expectations about the benefits or harms of their treatments, lack of energy and motivation, withdrawal and social isolation with feelings of hopelessness (140). DiMatteo et al. (7) explain that affective disorders, in particular depression, are among the most common disorders seen in medical practice, with depression occurring in at least 25% of patients and more likely in patients with significant health problems. The authors found in their meta-analysis of the effects of anxiety and depression on patient adherence, that anxiety had an unclear relationship with medication adherence. They suggest that anxiety can be heterogeneous and range from panic, which may have no direct effect on compliance, to obsessive compulsive disorder with generalised anxiety about health, which may promote compliance. Depression may be associated with higher rates of healthcare utilization and severe limitations in daily functioning (7) . For example, a meta-analysis by Meijer et al. (141) showed an independent relationship between depression and mortality and cardiovascular events in post-MI patients after adjusting for disease severity. Previous reviews were only able to provide unadjusted associations or limited estimates of adjusted associations.

DiMatteo (7) advises that once clear non-adherence is established, this should raise suspicion to clinicians of possible coexisting depression and steps should be taken to enhance medication adherence. There is a need for further research to determine whether treating depression will result in improved patient adherence (142, 143) but as the authors point out, this gives us the potential to improve medical practice, enhance patient functioning and improve health care outcomes. Ye et al. (144) have found that a conceptual

framework for medication non-adherence can guide assessment and treatment.

There is likely to be a vicious circle type link between depression and non-adherence whereby depression causes non-adherence and non-adherence further exacerbates depression. Therefore a clinical focus (7) concentrating research on testing the theoretical and clinical models to examine the direct effects of depression on patient adherence and patient outcomes is advised (7, 145). There is currently insufficient evidence from randomised clinical trials to demonstrate improved cardiovascular outcomes from psychological and pharmacological interventions in cardiac patients, but such interventions have been shown to reduce depression and improve quality of life (146).

The Patient Health Questionnaire-2

Summers et al. (147) advises that only psychometric instruments validated in the cardiac population should be used for depression screening and diagnosis, and any instrument that has been validated in this population can be justifiably used, as recent literature reviews have concluded that no particular instrument is superior to another in identifying depression. However, the PHQ-2 (patient health questionnaire) and PHQ-9 have proven to be the most specific among other instruments, and is recommended as a first step tool in identifying patients with depression, with a diagnostic interview afterwards(148),149). Barth et al. (149) state that there is insufficient evidence whether self report or clinical interview is the more precise predictor of depression.

The PHQ-2 which is a brief version of the PHQ-9 item questionnaire is recommended by the American Heart Association (AHA) prevention Committee of the Council on Cardiovascular Nursing (CCCN) as a first step approach for identifying currently depressed patients (150). The PHQ-9 is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders where the PHQ-9 is the depression module (151); major depression is diagnosed if five or more of the nine depression symptoms have been experienced for more than half the days in the past two weeks, and if one of the symptoms of depressed mood or anhedonia have been present. Other depression is diagnosed if two to four depressive symptoms have been present with one of the symptoms of depressed mood or anhedonia being present. If item nine “ thoughts that you would be better off dead or of hurting yourself in some way” is found to be present at all, regardless of duration, this counts as a diagnosis for depression (151). However, a recent study by Razykov (152) of one thousand and twenty two coronary artery disease outpatients concluded that item nine on the PHQ9 does not appear to be an accurate suicide screen, and the PHQ-8 might be more suitable for this group of patients. Kroenke (153) is wise to recommend that before making a final diagnosis, clinicians are expected to rule out physical causes of depression, normal bereavement, and a history of manic episode (the PHQ-9 is included in the Appendix B).

Development and psychometric properties of the Patient Health Questionnaire.

Previous researchers have shown that a single question about depressed mood has a sensitivity of eighty five to ninety percent for major depression and the sensitivity increases to ninety five percent by adding the question about anhedonia (154). The PHQ-9 was developed from the full PHQ (patient health questionnaire-which assess depression) which looked at six thousand patients from primary care clinics and seven obstetrics/gynaecology clinics in the United States. All patients completed the full Patient Health Questionnaire and the medical outcomes short form general health survey (155) while estimating the number of physician visits and sick days in the last three months. The construct validity was assessed using the twenty item short form general health survey, self reported sick days, clinic visits, and symptom related difficulty. The criterion validity was assessed against an independent structured mental health professional interview in a sample of five hundred and eighty patients (120), these patients were interviewed within forty eight hours of completing the full PHQ, and the mental health professional was blinded to the results of the PHQ. The authors state that patients that were re-interviewed were similar to patients that were not re-interviewed in terms of demographics, functional status and diagnosis.

The results of this study, and the validity of the PHQ-2, showed that of the forty one subjects who were diagnosed with major depressive disorder by the mental health professional, ninety three percent reported at least a score of one or greater which showed some depressed mood and ninety five percent reported some anhedonia. Patients with no depressive disorder (95% of them)

had a PHQ-2 score less than three, while most patients with a major depressive disorder (83%), had scores of greater than three (153). The PHQ-2 had a likelihood ratio for major depression nearly identical to the overall likelihood ratio for nine other depression instruments (2.92 vs. 2.86) in a meta-analysis of the literature (156). In this study they looked at questionnaires ranging from two to twenty eight questions with administration times of between two to six minutes. They found from the literature that if a case finding instrument was administered to one hundred patients in the community with a five percent prevalence of major depression, clinicians would find 31 patients would screen positive, four would have major depression and one with major depression would not be identified. No significant differences were found and the choice depends on the clinical situation and feasibility. Other authors have shown (122) that the predictive value of the PHQ-2 is similar to other instruments noting predictive value is not only related to measures of sensitivity and specificity but to the prevalence of depression.

Construct Validity-PHQ-2

Kroenke (153) found a strong relationship between increasing depression scores on the PHQ-2 and decreasing functional status on the short form general health survey, noting that the relationships observed were similar to previous studies where mental health functioning, social functioning and role functioning had the strongest inverse relationship (157), with a lesser direct relationship between pain and physical functioning. Results were the same for the primary care patients and the obstetric/gynaecology patients. Greater levels of depression severity were associated with an increase in healthcare utilization, sick days, and symptom related difficulties. The authors advise that

the PHQ-9 would still be the preferred instrument for diagnosing depressive disorders or assessing outcomes after treatment, however in many settings, when the aim is to screen for depression in combination with other questionnaires, as a first step approach or for research purposes brief versions are more suitable.

Kroenke (153) explains that this study builds on Whooley et al.'s previous study (154), where they looked at five hundred and thirty six mostly male veteran's mood over the past month. The answers to the questions were either yes or no to maximise sensitivity but this also decreases specificity, compared to the PHQ-2 which is more specific with only a modest decline in sensitivity. The authors point out that specificity is an important consideration when screening for depression particularly with large numbers, as false positives are difficult to handle efficiently with time and cost constraints (122). Monahan et al. (158) assessed the validity and reliability of the PHQ-9 and the PHQ-2 in three hundred and forty seven patients living with HIV/AIDS in Kenya, and recommended its use as well as Osorio et al.'s (159) recently carried out a study in Brazil on two hundred and twenty seven patients to consider if the two questions on the PHQ-2 were sufficient enough to screen for depression within a hospital context. They found that the PHQ-2 proved to have good psychometric properties in comparison to the PHQ-9 giving less false positives while being patient and clinician friendly in a practical setting. Arroll et al. (160) claim to have carried out the largest validation study of the PHQ-2 in a primary care setting at that time, where they looked at two thousand six hundred and forty two patients in Auckland New Zealand. The patients completed the PHQ-9 and the Composite International Diagnostic

Interview (CIDI) and the sensitivities and specificities were analysed for both the PHQ-9 and the PHQ-2 compared with the standard interview. They found that a PHQ-2 score of two or higher had good sensitivity but poor specificity in detecting major depression.

Conclusion on the PHQ-2

There appears to be controversy surrounding the use of routine depression screening in clinical practice (160) and good arguments for and against. Previously the United States preventive services task force believed there was enough evidence to support the case for routine depression screening (161). Gilbody et al. (148) argued that there was substantial evidence from their Cochrane Database Systematic review that routine screening for depression had minimal input on the detection, management and outcomes of depression by clinicians and advised against adopting this practice into guidelines and recommendations, until the costs and benefits have been sufficiently proven. There is, however, agreement that screening in high risk groups, such as chronic conditions like coronary heart disease, can be recommended if there are staff assisted depression care supports in place to ensure accurate diagnosis, and effective treatments with follow up care (148, 150, 161).

From the above literature there appears to be sufficient evidence for the use of the PHQ-2 in screening for depression in patients with coronary artery disease particularly if there is a correlation between depression and non-adherence.

Depression and adherence

Significantly lower rates of medication adherence have been reported in those with depression (7, 162-164). Systematic reviews have shown this previously (165). DiMatteo et al.'s meta-analysis correlated medical patients' treatment non-adherence with depression. Studies were included if they measured patient compliance and depression, involved a medical regimen recommended by a non- psychiatry physician to a patient not requiring treatment for depression, anxiety or a psychiatric illness. Twelve articles about depression and thirteen about anxiety met the inclusion criteria. The associations between anxiety and non-compliance were variable and non-significant as mentioned above. There was a substantial significant correlation between depression and non-compliance with an odds ratio of 3.0, with three times greater odds that depressed patients will be non-compliant using a binary cut off point of less than eighty percent was considered non adherent (47). Grenard et al. (140) found in their meta-analysis an odds ratio of 1.76 times depressed patients being non-adherent than non-depressed patients in thirty one studies with over eighteen thousand participants. The association was not as strong in studies that used pharmacy refill data compared to self-report and electronic cap measures. The main measures were self reported or physician reported, again showing the need for more studies with more objective measure of adherence.

DiMatteo (7) concluded non-adherence is a complicated phenomenon where decades of research have attempted to understand the variables connected in order to improve patient care, depression maybe one such important treatable variable. Positive beliefs and expectations are known to be essential for

patients to be adherent to healthy behaviours and prescribed medications. Depression often involves hopelessness and negative thoughts that make it difficult for patients to make the effort to take actions that they feel may not be worthwhile. Depression is often accompanied with social isolation which research has previously shown is an important factor in a patient's attempts to be adherent with medical treatments and to adopt healthy habits. The studies included in Di Matteo's meta-analysis are correlational studies that cannot explain whether depression causes non-adherence or non-adherence causes depression but this should not deter clinicians to be aware of depression as a risk factor for non-adherence. Grenard et al. (140) suggests factors influencing medication adherence are different to those that effect adherence to other therapies such as diet and exercise, and a focus on medication adherence was needed. Thus, they carried out a meta-analysis to evaluate the strength and direction of the association between depression and non-adherence. They included only studies that were performed in the United States, justifying this decision with the hypothesis that culture and the healthcare system are likely to influence the effect of depression on adherence. They noted that there is currently no gold standard for assessing medication adherence, so a variety of measures, such as self-report, electronic cap monitoring and examination of pharmacy records, were included in their review. They selected measures that were more objective of adherence or depression, for example pharmacy records over self- report, or a continuous scale over a dichotomised one that claims either adherent or non-adherent, which they suggest would provide more statistical power to detect effect.

Depression in Cardiovascular disease

The American Heart Association (150) and the European Cardiovascular Joint task force (166) have recognised that patients with coronary artery disease have a higher prevalence of depression than those without coronary artery disease, and over the past forty years, more than sixty prospective studies have looked at the link between depression and CAD. The literature shows that there is an independent association between increased depression and increased cardiovascular morbidity and mortality, and most studies have found the more severe the depression, the earlier and more severe the cardiac events (120,165). Rugulies (167) looked at cohort studies with clinical depression or depressive mood as the exposure and myocardial infarction or coronary death as the outcome. The conclusions that were drawn from this study were that depression predicts the development of coronary heart disease (CHD) in initially healthy people and there was a dose response relationship between depression and CHD.

Depression is three times more likely in patients after an acute myocardial infarction than in the general community and available studies suggest that depression is higher in patients with cardiovascular disease in the community than those without (168). It has been mentioned earlier in this chapter that researchers believe that there is a vicious circle between depression and coronary artery disease (150, 169, 170), which can lead to depression and consequently can lead to more heart disease.

Not all studies have shown a significant link between depression and prognosis when there is statistical adjustment for cardiac severity and some have tried to argue that this association is explained by cardiac disease severity (171). The literature appears more convincing that there is a pathophysiological link between depression and coronary artery disease (172). Researchers have found hyperactivity of the noradrenergic system as well as increased catecholamines which has an effect on the heart, blood vessels and platelets in patients with major depression (173) which is thought to be related to the increased sympathetic outflow in patients with ongoing depression. There have also been studies to show increased levels of catecholamine levels in the urine of patients with negative emotions and decreased perceived social support which correlate with high nor-adrenaline and low platelet serotonin, which are associated with myocardial infarction and depression (173).

Halaris (169) explains how interleukin-6, an inflammatory biomarker, and other stress hormones are associated with cardiovascular disease which can be caused by depression and lead to atherosclerosis, causing coronary heart disease. This can then lead to depression and a lack of joy and pleasure which can then lead to patients neglecting their health and possibly missing their medications. He proposes that psychiatrists and cardiologists work together in a multidisciplinary team to effectively treat patients with both conditions. Lett (174) supports this hypothesis, adding that behavioural and medication non-adherence add to the risk factors of further adverse events in patients predisposed to depression.

Depression and adherence in Cardiovascular Disease

Whooley et al. (156) in their study of over a thousand patients with stable Coronary artery disease from the heart and soul study found the association between depressive symptoms and adverse cardiovascular events was largely explained by behavioural factors mainly physical inactivity.

Oestergaard et al. (165) describes how single component interventions have failed to improve outcomes for patients with depression and how collaborative care and additional psychotherapy have been shown to provide more benefits for patients with depression than pharmacology alone. Both interventions have been shown to provide benefits in the short term, with psychotherapy having the most effect in the long term, preventing relapse. They state that conclusions regarding the effects of medication adherence improvements are fairly certain, although again a literature search did not find a direct objective measure of medication adherence (175) which may be due to the practicalities and ethical considerations of taking direct objective measures in this vulnerable group of patients. Table 3 below shows a review of the literature of depression and adherence in cardiovascular patients.

Table 3 - Studies measuring the relationship between depression and medication adherence in coronary artery disease patients

Author,year, country	Sample setting	Study design	Sample Size	Depression and measures of adherence.	Results	Comments
Carney et al., 1995. U.S	Patients 65 yrs or over undergoing an elective diagnostic coronary angiogram.	Prospective cohort study	55 pts	Diagnostic and statistical manual of mental disorders, 2 independent physicians, Electronic monitoring device.	10 of the 55 pts were diagnosed as having depression and adhering to aspirin twice a day only 45% of the time while non-depressed patients adhered 69% of the time $P<.02$	This study used an objective measure of adherence but the numbers were small and there is no way of knowing did the patients actually ingest the aspirin.
Carney et al., 1998. U.S	Patients < 75 yrs with Coronary Artery Disease.	Prospective cohort study	65 pts	Electronic Adherence Monitor. Rose Angina Questionnaire, Autonomic Perception Questionnaire (APQ), Beck Depression Inventory (BDI), State –trait anxiety Inventory.	Symptomatic patients were less adherent 62.4% days, asymptomatic patients were adherent 77.3% days $P<0.03$. Symptomatic patients were more depressed $P<.10$. Approaching significance in a small sample. Symptom status was not an independent predictor of adherence when controlling for depression.	Patients over 75 yrs were excluded. Symptomatic patients were less likely to be married. Social support, beliefs about illness and medicines were not measured and may be confounding variables. Depression may have been a factor in reduced adherence.

Gehi et al. 2005 U.S	CHD patients from 2 veteran affairs medical centres, 1 university medical centre, 9 community health clinics.	Prospective cohort study	940 pts	PHQ-9. Computerised interview schedule iv. Social support. Self report non- adherence of - Not taking meds - Forgetting - Skipped dose	204 pts-(22%) had current depression, 7% of all patients reported non- adherence and theses with depression were more likely to report non- adherence-adjusted OR (95% CI 2.2(1.2-3.9)P value .009. PHQ .003 for trend.	After adjusting for confounding variables, depression remained associated with all three measures of non- adherence.
Kronish 2013, U.S	Acute Coronary Syndrome patient	Prospective cohort study	169 patients	Beck Depression Inventory (BDI) Medication event monitoring device(MEMS)	23% had poor adherence to aspirin and poor adherers were more likely to be depressed P=0.01 Of the depression vulnerabilities only role transitions P=0.02 and interpersonal conflict predicted poor adherence.	Patients included in the study were aware that aspirin adherence was being measured therefore this was likely to improve adherence.
Lin et al., 2012 U.S	14 Group Health primary care clinics	Randomised Controlled trial.	214 patients	PHQ-2, HBA1c,Blood pressure, cholesterol levels, pharmacy refill data	15% of patients screened positive to the PHQ-2. No medication adherence differences were observed between the intervention group and the usual care group.	Medication was high at baseline for both groups 79-86% and it is not clear how many of these patients were actually CAD patients.
May et al., 2010. U.S	ACS patients from the (IHCS) Intermountain	Prospective cohort	585 patients	ICD-9 depression scale.	All time points 6mths, 1yr, 18mths, 2yrs-those	Refill data doesn't necessarily mean

	Heart Collaboration Study			Pharmacy refill data measure of adherence.	with depression had significantly lower medication adherence compared to those without depression.	patients ingested the Aspirin.
Rieckmann et al., 2006 U.S	ACS patients	Prospective cohort	165	BDI scale at baseline and 3 mths post MI. Electronic monitoring device	Persistently depressed patients were significantly less adherent than non-depressed patients $P<.01$	Patients were aware that aspirin adherence was being monitored.
Ziegelstein (2000) U.S	Acute coronary Syndrome patients	Prospective cohort study	204 patients	Beck Depression Inventory (BDI) Clinical interview for depression, Medical Outcomes Study Specific Adherence Scale (MOSSAS)-self report adherence.	15.2% patients with major depression reported significantly less adherence to their medication $P<0.03$. Also low fat diet $P<0.01$, regular exercise $P<0.03$ and increasing social support $P<.003$	The total score for adherence behaviours was significantly lower in patients with major depression than those without $P<.001$. Validity of self report data may be influenced by a more negative description of self in depressed patients.

PHQ-9=Patient Health Questionnaire 9, PHQ-2=Patient Health Questionnaire 2, ACS=Acute Coronary Syndrome, MI=Myocardial Infarction

Literature on depression and adherence in heart disease was identified using key search terms in PubMed, and checking Google Scholar for other relevant articles which cited the studies found with the PubMed search. More details on keywords and searches are available in Appendix B.

Carney et al. (163) looked at major depression and medication adherence in patients sixty five or older with a diagnosis of Coronary Artery Disease. He acknowledged that depression is less common in the elderly patients than younger patients (176), but a high percentage of medical patients suffer from clinically significant depression, with fifteen to twenty two percent of CAD patients suffering from depression (163). Carney et al. (134) also noted that depression was associated with a higher rate of non-adherence in younger chronically ill or disabled patients, but research on the effects of depression on adherence in the elderly was lacking. In this study by Carney et al. (134) they found that major depression was associated with non-adherence in ten of fifty five patients over the age of sixty five with a diagnosis of CAD. Although this study used an objective measure of adherence (i.e. a medication monitor), the sample size was relatively small and there is no way of knowing if the patients ingested the aspirin. In a separate study (177) they then looked at differences in medication adherence between symptomatic and asymptomatic patients with Coronary Artery Disease with a view to determine if patients with asymptomatic CAD were less depressed than patients with symptomatic CAD. They explain that previous studies have shown asymptomatic conditions have related to poor adherence in other populations, but depression is more common in patients with symptomatic CAD. Their results concurred with previous studies showing asymptomatic patients were significantly less depressed than symptomatic patients using the Beck Depression Inventory scale (BDI) and depressed patients were more likely to be less adherent, however the relationship was only approaching significance in this small study. Symptoms were not an independent predictor of

adherence after controlling for depression in a multiple regression model. They concluded that depression may be a factor in non-adherence in symptomatic patients but other factors must be considered. Symptomatic patients were less likely to be married therefore may have less perceived social support. Finally they acknowledge limitations of this study are measures regarding beliefs about illness or medicines were not measured, which are likely to be important factors.

Lin et al. (178) conducted a randomised controlled trial looking at treatment adjustment and medication adherence in complex patients with diabetes, heart disease and depression. They developed a patient centred team based intervention, with the aim of improving patient self monitoring, medication adherence and treatment adjustments in patients with multiple conditions and depression, with poor control of their hypertension, blood glucose and cholesterol. Patients were eligible if the blood pressure and blood values showed poor control and they had a depression score of ten or higher on the PHQ-9. Patients were then randomised into either the usual care group or the intervention group. Pharmacy refill data was used to measure medication adherence twelve months before and after baseline. Medication adherence was found to be unusually high in both the intervention group and the usual care group (79-86%) as can be seen in Table 3. There was no significant difference in adherence between the control group of usual care and the intervention group (which was team care), a surprising result to the authors. Medication alterations and initiations were significantly higher in the intervention group, particularly in the first two months after randomisation and

the authors point out that previous observational studies have found that lack of physician treatment adjustments can be more problematic than medication adherence among patients that are poorly controlled with their diabetes or heart disease (148). This study did show improved self monitoring, glucose, cholesterol and blood pressure control and recognised the effect of the team care approach of monitoring patient progress, supporting self-care activities and a multidisciplinary case review all contributed to better control. The authors suggest that the study shows an integrated approach in treating mental and physical illness can be applied to most patients with chronic conditions regardless if they have depression or not.

Kronish (179) looked at the psychosocial impacts on medication adherence in Acute Coronary Syndrome (ACS) patients that were recruited within one week of their coronary event. Patients' depression was measured with the Beck Depression Inventory (BDI) scale and adherence was measured with a medication event monitoring device on the aspirin container (TABLE 3). Other measures used were the Dysfunctional Attitude Scale (DAS-24), the pleasant event schedule for the elderly, role transitions and interpersonal conflict. The results from this study showed twenty three percent of patients were non adherent (took aspirin <80% of the days) to their aspirin using the medication event monitoring device which shows how many times the aspirin container was opened each day, although it is acknowledged that this does not necessarily show ingestion of the aspirin. It is possible that this cohort of patients may have a higher than usual adherence rate as they were recruited within one week of their Acute Coronary Syndrome (ACS) event and were

also aware that adherence was going to be measured. The study found that poor adherers to their aspirin were significantly more likely to be depressed- ($P=0.01$) but of the depression vulnerabilities only role transitions and interpersonal conflict predicted poor adherence when adjusted. The authors explain that depression is a multifactorial psychological disorder that can arise from a combination of genetic, biological and environmental factors in patients with underlying vulnerabilities. The authors hypothesised that patients who are not inclined to schedule pleasurable activities may also have low self-care activities including adhering to their medications. They also hypothesised that patients who experience psychosocial vulnerabilities, through either interpersonal conflicts or major life events, may lack the social support and habit that supports medication adherence.

Ziegelstein et al.'s study (180) previously had looked at over two hundred patients recovering from Acute Coronary Syndrome (ACS) to determine whether patients with depression were less likely to follow recommendations to reduce cardiac risk including adhering to prescribed medications. When interviewed at four months after their acute episode, patients that had been diagnosed with at least mild to moderate depression with a BDI score of greater than or equal to ten or with major depression determined by the SCID during their recovery time in hospital, reported less adherence to a low fat diet, regular exercise, stress reduction and regular socialising than non-depressed patients. Patients with major depression or dysthymia reported less medication adherence. Patients who dropped out of cardiac rehabilitation were found to be more depressed, anxious, hyperchondriacal and socially

introverted at enrolment than those that completed the programme. The authors discuss one of the limitations of this study is all measures of adherence were self reported and not independently verified, noting that self report data may be influenced by a more negative description of one's self in depressed patients. Other authors have argued that this negative response bias observed in depressed patients may be a more realistic value (181). Ziegelstein et al. (152) recommend further research is required to establish whether treatments on depression or adherence interventions will improve the prognosis for Acute Coronary Syndrome patients.

Only four studies looked at coronary artery disease, two of these used self reported measures of adherence (164, 180) and two used the more objective measure of a medication event monitoring device (177, 179) see Table 3. Although the medication event monitoring from the containers does not necessarily mean the medication was ingested.

Conclusion

The research from the above literature shows significant associations between depression and medication adherence in different disease groups including Coronary Artery Disease. These studies show consistency whether the disease is chronic or acute, symptomatic or asymptomatic. The authors in table 3 agree that depression is multifactorial and may have other influencing variables such as social support, beliefs about illness and medicines that need to be considered. The inconsistency of measurements between studies also makes it difficult to compare studies with no gold standard measure of

adherence or depression, although there appears to be more use of validated questionnaires, like the PHQ-2, that are brief and appropriate for use in clinical settings with other questionnaires. There are also improvements in measuring adherence with more objective measures, rather than relying on self report which researchers agree is generally over reported and does not take into account patients forgetting. While depression has been consistently associated with poorer adherence, it is unclear how or whether it is related to beliefs about medicines or illness, or whether it may account for the associations between these cognitive factors and adherence.

CHAPTER 5-Social support

Chapter overview

This chapter will look at social support and its effect on health, cardiovascular disease and adherence. Defining social support and the theory behind it, reviewing studies of social support and its effect on health, by biological mechanisms, but also behavioural factors, including adherence. Then, reviewing studies that have looked at correlations of social support and adherence, in patients with coronary heart disease. Finally, critiquing the previous literature, the significant relationship between social support and adherence that has led researchers to suggest that adherence is an important mediator between social support and health (182).

Defining social support

Yohannes (183) states that there is no precise definition of social support in the literature but uses the Umberson et al. (184) definition of “the commitment, caring, advice and aid provided through relationships or network of people”.

Langford et al. (185), describes social support as the assistance and protection given to others, where assistance may be tangible such as financial aid or intangible as in emotional help. Protection may come in the form of shielding people from adverse events or the effects of life stresses. The authors point out that social support is a resource given with the expectation of reciprocation, normally exchanged between at least two individuals.

DiMatteo (182) has described in his meta-analysis of social support and patient adherence to medical treatment, how the relationship between social support and health has received a great deal of attention. He and other researchers point out that there is an effect on the immune, endocrine and the cardiovascular system, influencing health maintenance and recovery from illness or injury. The exact mechanism of how social support has an effect on these systems is still not completely understood.

Lack of social support is associated with increased morbidity and mortality in patients with ischaemic heart disease (186, 187), and Uchino et al. points out that the most compelling evidence to date of the effects of social support on all-cause mortality has been shown by Holt-Lunstad et al. (188) where a meta-analysis of the existing literature found that perceived support was related to significantly lower risk even after statistically controlling for other variables such as demographics, health behaviours, exercise and obesity.

Patients with low practical social support have shown a correlation with lack of adherence (189), this was shown in the literature review of 122 studies that were found to correlate social support with patient adherence to medical regimens, again these studies mainly used self reported adherence rather than an objective measure. Those who do not receive practical social support (e.g. reminders, assistance); have a relative risk for non-adherence almost double that of those who do receive practical support. Furthermore, adherence is 70% higher in patients from cohesive families, but over 50% lower in patients from families in conflict (189). These results highlight the impact of social and emotional factors on medicine adherence.

The Theory of Social Support

Researchers have recognised the positive relationship between social support and health for many years including patients post myocardial infarction. The theoretical foundations of social support include social comparison, social exchange theory and social competence. Social comparison theory believes that people develop their self-concept by comparing themselves to others in their close reference groups which enhances coping abilities, emotional adjustment, self-esteem and emotional well-being. However it appears to depend on social exchange (185). Social exchange theory describes human behaviour as an exchange of mutually rewarding activities, where there is a positive relationship between life satisfaction and the exchange of social support. If there is social comparison and social exchange, Langford et al. (185) suggest that this implies there is some degree of social competence. Social competence is described as the ability to effectively interact with the environment and is essential in the building and maintenance of relationships which leads to social, psychological, physiological health and prevents social isolation which can lead to negative health (34, 186, 190). Social climate is defined as the personality of the environment and it is within this climate of assistance and protection that the theoretical foundations of social comparison, social exchange and social competence operate (185) .

There are four attributes of social support that have been described by Langford et al. (185). Emotional support, which is generally considered the most important, involves love, trust, empathy and caring. Instrumental support, which is tangible and concrete, such as financial assistance or practical help, which may also suggest caring and love. Informational support

which involves the giving of advice, guidance and helpful information, and lastly, appraisal support where some-one offers information that allows the person to make an informed decision on their own, for example “I trust your judgement “ or “you are doing the right thing”.

Some authors argue that one of the most effective forms of support is invisible support where the person is unaware of the support and therefore promotes a sense of self-efficacy (191, 192). In a study carried out by Bolger et al. (192) where they looked at data from a daily diary study of support provision and receipt in couples, they found that many supportive actions reported by providers were not reported by recipients, and this type of invisible support can promote adjustment to major stressors. A later study (191) to investigate this type of support looked at two hundred and fifty seven females before a stressful speech task where a peer provided either visible or invisible support either practically or emotionally. Invisible support either practical or emotional was found to be more effective in reducing emotional reactivity than visible support. There has been extensive research showing the benefits of a romantic partner particularly for men (193), with some researchers hypothesising that this is due to men being able to delegate emotional stress (185) whereas women may be better providers of support and more likely to seek it out and therefore gain more benefit (188). Other researchers argue that higher coronary artery disease is linked to more ambivalent (perceived as having upsetting aspects as well as positive) relationships between couples than those that are perceived more positive (187). The researchers hypothesise the reason for no link between negative social support and

coronary artery disease is people are unlikely to stay in a relationship that they perceive completely negative. Early familial support has also been shown to be an important factor in peoples' abilities to develop social competencies and thus coping skills which are linked to behaviours, habits and psychological health (194). This may also have a role in adherence.

Researchers more recently have argued for a distinction on the context of support in understanding the links between social support and health, stating that primary and secondary groups differ (195). Primary groups which are considered typically long lasting, informal and consist of significant others are thought to be more effective for emotional support. Whereas secondary groups are considered less personal and members can exit or enter at their own discretion, are likely to be more formal and are thought to be more effective for informational support (195). This can be seen when a patient with a chronic disease may gain more benefit from information from a secondary support, for example a health professional rather than a spouse who may lack insight into their partners pain of physical symptoms which can lead to problematic support (196). The same author suggests that a sense of "mattering" is also an important factor in social support that is linked to self-esteem and control.

Perceived and received support

Researchers have also made a distinction between perceived and received support where perceived support is a recipients subjective judgement that they will receive the support if or when required, whereas received support is supportive actions or an exchange of resources emotional or instrumental

given when needed (197). Perceived support has been consistently associated with improved mental health whereas received or social integration have not (198). It appears from the literature that it's the perception of the support whether it is received positively or negatively that has the influence on health, and researchers have described the importance of perceived responsiveness where it seems beneficial if it appears responsive to the recipient. Uchino et al. (197) points out that it is one of the most researched psychosocial factors that has an influence on health outcomes, in particular low levels of support have higher rates of mortality in cardiovascular disease (199).

Laboratory studies looking at cardiovascular reactivity and received social support have repeatedly found a positive correlation between the two and it is hypothesised that receiving support over time has a long term positive cardiovascular effect (200), although recent laboratory reactivity findings have not been able to consistently identify the negative mechanisms unsolicited support can sometimes have. Whereas there seems to be significant variability between received support compared to perceived support and health (188), researchers suggest that this may be due to negative psychological mechanisms if the recipient feels a threat to their independence and this reaction may cancel out the positive influence of actually receiving support.

Rational Regulation Theory is another theory that hypothesises that the link between perceived support and health comes from people regulating their

emotions through ordinary conversations and shared activities rather than conversations on how to cope with stress (177).

Social support and Health

In general Uchino et al. (197) suggest that the available literature shows the positive influence of perceived or received social support on cardiovascular, endocrine and the immune system even when controlling for other variables such as life stress, depression and anxiety. This review reflected on a workshop that brought together experts working in the area of social support and cardiovascular disease. They noted three distinct ways that social support might relate to cardiovascular disease. Support impacts directly on emotions, which in turn produce haemodynamic responses. Support affects behaviour which influences physiological responses, and support directly alters cardiovascular risk indicators. The author advises though that researchers may need to measure these processes over time as most studies use a cross sectional design assuming that the health related state is measured accurately at that point in time when there may be other variables such as time of day (circadian rhythm) or the environment (negative/stressful) . Although these studies are costly and time consuming they are important given the associations between social support and cardiovascular disease and may take into account the sequence of events that lead-up to an illness.

Biological Pathways

Social support has been found to have a positive influence on the cardiovascular system as well as the neuro-endocrine and immune system (198) lowering levels of inflammatory markers, stress hormones and cardiovascular reactivity measured by blood pressure and heart rate. Uchino et al. (201) also looked at the relationship between positive, negative and ambivalent relationships with telomeres (which are found on chromosomes and deteriorate with the aging process). They looked at one hundred and thirty six people aged 48-77yrs from a community sample of patients and found that the higher number of ambivalent relationships the shorter the telomeres as measured in peripheral blood. They also found that gender moderated these links with more of a link found in women. They suggest that cellular aging provides the framework for measuring telomeres as they help to promote the stability of the chromosome but with each successive replication of the cell, telomeres shorten which can ultimately lead to unregulated cellular activity. Importantly shortened telomeres have been linked to three times more mortality risk from heart disease and eight times greater risk from infectious disease up to twenty years later (182). The authors point out that the theory behind the harmful effects of the ambivalent relationships is that they are unpredictable and therefore associated with more interpersonal stress, they also point out that age did not moderate the links between telomeres and relationships. This study provides mechanistic information on the biological link between social support and disease morbidity and mortality.

Measuring social support: The ENRICHD Social Support Instrument - ESSI

In response to the large amount of research showing the effects of psychosocial influences on patients' recovery post myocardial infarction the Enhancing Recovery In Coronary Heart Disease ENRICHD trial clinical trial was initiated. This was a multicentre, randomised, trial looking at a psychosocial intervention on patients with clinical depression or social isolation and the effects on cardiovascular morbidity and mortality (202). The study used the ENRICHD social support instrument which is a measure derived from the medical outcomes survey and previous work that has shown the influences of social support on health outcomes (202) (203, 204). The investigators stated that existing studies didn't provide a clear guide of the social support being measured, for example, marital status, type of support and the clinical outcomes associated. This led the investigators to develop the seven item questionnaire with a scale of one to five- (see Appendix B) to accurately assess social support (202). Before this study no clinical trial had tested the effects of increasing social support on clinical endpoints in patients post MI.

Vagilo et al. (204) carried out a study to test the validity and reproducibility of the ESSI in one hundred and seventy four patients undergoing percutaneous coronary intervention (PCI). Patients were administered the ESSI with the SF-36 mental health and social functioning subscale which was a widely used generic measure of health status and the Seattle Angina Questionnaire (SAQ) which is a disease specific measure of health status for patients with coronary disease, at baseline and every month after for six months post percutaneous coronary intervention (PCI). The authors state that in the absence of a gold

standard measure for social support, construct validity was assessed by comparisons of the ESSI with depression, social mental and physical functioning, symptom severity and quality of life in order to support the use of the ESSI in examining the relationship between social support and cardiovascular outcomes. Test re-test analysis carried out at five and six months showed no significant differences in the ESSI scores and excellent reproducibility. The mean ESSI score at baseline among depressed patients was significantly lower than those that were not depressed, as well as people that were living alone rather than living with someone had lower ESSI scores. The questionnaire showed acceptable internal consistency and correlated with other social support instruments, while also suggesting that patients with greater social support have greater social functioning, improved symptom control and better quality of life (196). Overall this study found that the ESSI is a valid and reliable measure of social support in coronary artery disease patients.

Social Support and adherence

Researchers have hypothesised that the link between social support and health may be patient adherence to healthy behaviours as well as adherence to medications (167). Adherence involves patients accepting they have a condition and can have an effect on the outcome by following advice and treatments. As discussed previously non-adherence rates can range between 25% - 75% and can have a significant effect on outcomes. Adherence is thought to be mediated through family support and friends by improving optimism and self-esteem, buffering the effects of ill health, reducing

depression and giving practical assistance. Researchers agree that quantitative studies exploring the effects of the different types of support, for example marital, practical and emotional support on adherence are essential in understanding the link between social support and health (179-181).

Di Matteo (182) carried out a meta-analysis of studies that looked at social support and patient adherence across one hundred and twenty two studies. He found a significant relationship between adherence and all types of support including practical, emotional, family cohesiveness, marital status and living arrangements. The risk for non- adherence was almost twice as high among patients with low practical support compared to those with high practical social support, however, smaller samples reported significantly higher correlations of practical support with adherence than the larger samples, possibly eluding to more bias in the smaller samples. However, the author points out that there would have to be one thousand and eight hundred unpublished research papers that found no effect of practical support on adherence to make the P value of 0.05 insignificant. Studies using self reported adherence showed higher correlations than those that did not use self reported adherence. The odds of adhering were found to be three times higher among patients in close cohesive families than families experiencing conflict, and the odds of adherence were also higher if patients were married, but support such as practical, emotional and family cohesiveness were significantly stronger than marital status or living arrangements. He also notes that the presence of other people does not matter as much as the quality of the relationships which has been supported recently by Yohannes (183) who

explains that strong social support networks enhance self efficacy, identity and self management behaviours including medication adherence. Group activities improve physical and psychological health, which in turn can reduce cardiovascular disease. Whereas, a non-supportive social network can interfere with healthy habits limiting the patients time for healthy behaviour and introducing stress.

DiMatteo states that there is surprising consistency in the relationship between social support and adherence in the literature suggesting that the link between social support and health is mediated through adherence, although he acknowledges that adherence is mainly self reported and the significance is reduced when other measures of adherence are used (182), there is no evidence that the mean effect of the result is due to self reported adherence. He also acknowledges that although social support influences adherence, it is also possible that adherence influences social support as patients that adhere are likely to receive more support for their efforts than those that are non-adherent. Conversely, lack of social support or the wrong type of support can interfere with healthy lifestyles and introduce stress that compromises the healthy behaviour and attitude required for adherence (175,176).

Although patient adherence is related to social support lifestyles and outcomes, researchers accept that patient depression is strongly related to both adherence and social support and must be considered as a possible mediator.

Social support and medication adherence in patients with Coronary Artery Disease (CAD)

The table below shows the studies from 2000 to the present date that could be found measuring social support and adherence in coronary artery disease.

TABLE 4- Studies of the relationship between social support and medication adherence in patients with CAD

Author,year, country	Sample setting	Study design	Sample Size	Social support and measures of adherence.	Results	Comments
Aggarwal,(2010) U.S	Patients admitted to a university cardiovascular service (cardiology/cardiac surgery).	Cross sectional baseline analysis.	1,432 pts	Questionnaire asking if the patient would have a paid professional caregiver or a non-paid family caregiver. Adherence was self reported if they missed a dose in a week in the last 6 months.	One in four patients admitted to being non-adherent to their medication. Patients who were planning to have a paid caregiver were 40% less likely to be non-adherent than their counterparts. Significance remained after adjustment for confounders and co-morbid conditions(OR=0.49:95 %CI=0.29-0.82)	Paid caregiving was associated with significantly less likelihood of non-adherence to medications among women but not men. There was a similar relationship with informal caregiving but not significant.
Gehi et al., (2005) U.S	CHD patients from 2 veteran affairs medical centres, 1 university medical centre, 9 community health clinics.	Prospective cohort study.	940 pts	Social support measured with one question. Self reported medication adherence.	7 % of patients reported non-adherence. Poor social support was associated with non-adherence-	The authors acknowledge that adherence was self reported and probably higher than the general

					OR,2.05;95% CI.-1.2-3.2	population.
Molloy et al., (2008) UK	Acute Coronary Syndrome patients from CCU.	Prospective observational clinical cohort study.	262 pts	Social support measured with questions on emotional and practical support. Self reported adherence measured via telephone interview at 12 mths.	29.8% of patients had no practical supports. Patients with more practical support were more likely to adhere to medications which remained significant after adjustment for age, gender, marital status, clinical risk profile and depression OR 2.12,95%CI 1.06- 4.26,P=.034	Measure of adherence was self reported and the study suggests that if the patient admitted to forgetting one dose this was considered non- adherent. A sub- study found partner stress predicted medication adherence OR 2.89 95% CI=1.21,6.96

It can be seen from the table above that Aggarwal et al. (205) found a significant correlation between patients who reported planning or having a paid caregiver and a forty percent less likelihood of non-adherence to cardiac medications. Cardiac patients often rely on reminders from family, friends or paid caregivers with daily tasks such as medication taking and the authors speculate that paid givers are more accountable and trained than informal or family caregivers. The previous literature on this appears conflicting where the presence of a spouse increases adherence in heart failure patients (206), but in contrast, another study among patients with kidney disease found patients who relied on a family member were more likely to be non-adherent (207). The authors (186) suggest that training family caregivers with aids such as pillboxes and automated alerts may have the potential to enhance medication adherence in cardiac patients.

In the study by Gehi et al. (164) they found an association between social support and self reported non-adherence to cardiovascular medications, even though they only asked one question assessing social support “ Do you have some-one you feel close to, some-one in whom you can trust and confide?(yes/no)”. Also, Gehi acknowledges that the self reported rate of seven percent non-adherence is unusually low, therefore is not likely to be representative of the general cardiovascular population pointing out that patients included in this study were likely to be more motivated in adherence behaviours as they were taking part in clinical study.

Molloy et al. (208) notes that the odds ratio of death in the first six months following myocardial infarction were 2.9 times more likely in patients who lacked social support than those with two or more sources of support, independent of clinical and socio-economic factors. Williams et al. (209) found that unmarried or patients that lacked a close confidant were three times greater risk of dying, five years post coronary angiogram than those that were married or had a close confidant. This is supported by a recent look at the data of the perceived social support that was measured in the ENRICHD study which showed a direct relationship between social support and clinical outcomes over four and a half years following myocardial infarction. This relationship was independent of other risk factors but only in patients without elevated depression scores (210). In the Molloy et al. (201) study, emotional and practical support were assessed within the first five days of admission using measures devised by Berkman et al. (211), patients were asked “can you count on anyone to give you emotional support” and “when you need extra help, can you count on anyone to help you with daily tasks like shopping”. Adherence to medication was assessed by telephone interview at twelve months post hospitalisation. If the patient reported any problems with missing doses or adherence this was considered non-adherent. Half of the patients were considered adherent at twelve months following discharge. There were two hundred and two men and sixty women in the study and there was no significant difference in practical support found between the two genders. Unmarried patients were more likely to have no practical supports available to them. The final results of the study were that patients with two or

more sources of practical support were two fold more likely to be adherent to their medications as well as adherent to cardiac rehabilitation, although there was no association with emotional support. This correlation was no longer significant when controlling for depression.

In summary, there were only three studies that measured social support and non-adherence. All found social support predictive of adherence but none of these studies used an objective measure of adherence.

Conclusion of social support and medication adherence

Social support has been defined as the assistance and protection given to individuals which may be tangible as in financial aid or intangible as in emotional help and this protection may protect people from the adverse events of life stress, it is generally given with the expectation of reciprocation (185) (208). The literature shows that some of the effects of social support are; personal competence, coping ability, positive affect and a sense of stability, recognition of self-worth, decreased anxiety and depression, while promoting healthy behaviours and physical and psychological well-being. One of these healthy behaviours is medication adherence, where studies have shown a direct correlation between social support, both emotional and practical, and medication adherence (164, 212). Uchino (197) points out that although social support has proven to be a robust predictor of mortality and morbidity decades of research have been unable to demonstrate the mechanisms responsible for these links adequately and advises strongly on improving the statistical design of studies, specifying the difference between perceived and received support and looking for correspondence between self

reported affects and biological measures. Direct associations between low social support and activation of inflammatory markers has been linked to the physiological processes involved in poorer outcomes of coronary artery disease patients (213). It can be seen from the above table that there appears to be a lack of research on social support and medication adherence in coronary artery disease patients, with no studies measuring a direct measure of medication adherence with other important variables such as depression and beliefs about illness and medication.

CHAPTER 6 - The Present Study

Introduction

This thesis is a review of the current literature in medication adherence in particular, focusing on medication adherence in patients with coronary artery disease. This included examining the measures of medication adherence explored in previous studies. Using the psychological variables that have previously been identified in systematic reviews, the relationships between beliefs about medicines, beliefs about illness, depression, social support and aspirin adherence were explored.

The above literature demonstrates how beliefs about medicines, beliefs about illnesses, depression and social support all purport to have an influence on adherence to medications. However, the research is limited in coronary artery disease patients and also limited by the measures of adherence used, and non-adjustment for potentially mediating effects of each of the variables. Any interventions to improve adherence should be derived from the best predictors of adherence in the population, which evidence suggests are the psychosocial variables listed above. However, few studies have simultaneously measured these variables while using a direct method of adherence measurement (214) and the literature appears somewhat conflicting at times. The proposed study provides a unique opportunity to assess predictors of a direct-measure of adherence, with the hope that it will provide information that will guide subsequent intervention–planning in promoting medication adherence.

Previous measures of adherence

There are limited examples of objective measures of adherence particularly in CAD patients and there are no studies that measure aspirin adherence objectively while also looking at the psychological variables of depression, social support and beliefs about medicines and illness to our knowledge at present. The current study will therefore look at these psychological factors of adherence in combination with a validated objective measure of aspirin in blood serum.

Aim

The aim of study is to determine the best psychological predictor of adherence to aspirin therapy as measured by the best available assay available. To do this, the plan was to recruit patients who took part in the aspirin effectiveness in Ireland study with stable coronary artery disease who have been prescribed aspirin and who took part in the national study looking at aspirin adherence.

From this cohort, it is expected to identify approximately 20% of patients who are non-responsive to aspirin, as this is the percentage of patients that were found to be non-responsive in the national study of 700 patients with stable coronary artery disease (using the same assay and cut off point of 2.2ng/ml (215). It is then proposed to characterise the reasons for lack of response in this cohort. Specific objectives are as follows:

- Recruit over 100 patients from the national study of aspirin effectiveness in Ireland.

- Assess adherence using the Thromboxane B2 ELISA assay.
- Correlate the results with the results from the psychological questionnaires.

Hypotheses are as follows:

- 1) Correlation between self-report non-adherence, (measured by asking patients have they missed any aspirin doses in the last week, or do they ever forget to take, or purposely miss doses), and the current most specific and viable assay response to aspirin using thromboxane B2 (216).
- 2) Psychological aspects which have predicted adherence in previous studies, which may provide useful pointers for interventions in the future, specifically.
 - Beliefs about medicines –that patients with negative beliefs about medicines will have a direct correlation with an ineffective response to aspirin (above the cut off point for thromboxane B2 of 2.2ng/ml) suggesting non-adherence to aspirin.
 - Beliefs about illnesses – patients with a negative view of their illness and its treatment control will have a direct correlation with lack of aspirin response (above the cut-off point of thromboxane B2 2.2ng/ml) thus suggesting lack of adherence to their aspirin.
 - Depression – higher scores of depressive symptoms will correlate directly with a lack of aspirin response (above the cut-off point of thromboxane B2 2.2ng/ml) indicating lack of adherence to aspirin therapy.

- Social support – lower perceptions of social support will correlate directly with a lack of response to aspirin therapy (above the cut-off point of 2.2ng/ml for thromboxane B2) indicating lack of adherence to aspirin therapy.

Exploratory multivariate analyses will also be used to determine which of the above predictors of adherence is the most important in patients with CAD.

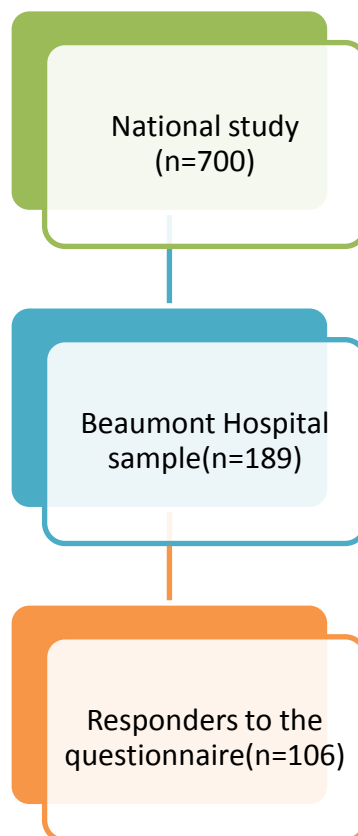
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Chapter 7- Methods

This chapter will describe the sample, design, measures, procedure, ethics and statistical analysis that were used in the current study “An exploration of the Psychological Indicators of Aspirin Adherence, in Patients with Stable Coronary Artery Disease, Using a Direct Assay Measurement”. It will also explain the initial national study “Aspirin effectiveness study in patients with stable coronary artery disease” and the inclusion exclusion criteria that were used for both the national study and the sub-study.

The national study had a total of 700 patients (189 from Beaumont) recruited in total. At the time of commencement of the sub-study, the national study had 600 patients recruited (156) from Beaumont who had already consented to the national study and had their blood sample taken. These 156 patients from Beaumont were sent their psychological questionnaires in the post rather than wait for their next outpatient visit as patients who are stable are more often than not discharged back to their general practitioner or would not have another outpatient appointment until the following year. The subsequent 33 patients were recruited from Beaumont outpatients department and were asked the questionnaires face to face.

Flow sheet of studies



Sample

National study-Aspirin Effectiveness in Stable Coronary Artery Disease Patients in Ireland

The inclusion and exclusion criteria for the national study are listed below.

Inclusion Criteria:

- Age 18 years or older
- Patients with documented CAD (defined by the presence of lesions on coronary angiography, history of myocardial infarction, or positive stress test)
- Current treatment with any dose of aspirin daily for a minimum of 3 months

- Able to provide written informed consent based on competent mental status.

Exclusion Criteria:

- Myocardial infarction, unstable angina or stroke during the preceding three months
- Platelet count <125,000/mm
- Known haematological disorder such as myelofibrosis
- Active malignancy on current chemotherapy or a recent (<3 months) diagnosis of cancer

The cut off point for an effective Thromboxane B2 response for this study was >2.2ng/ml as defined by Maree AO et al. (217).

The main findings from this study and previous similar studies were that patients who were younger in age, overweight, and had a high alcohol intake were most likely to have an inadequate response from their aspirin therapy (81).

Ethics

As the sample population were all patients of Beaumont Hospital, an application for approval was submitted to “Beaumont Hospital (Medical Research) Ethics Committee” on the 21st of May 2012 and reviewed on the 15th of June 2012. The Ethics Committee responded on the 28th of June 2012 requesting some clarifications and amendments (See Appendix B). The main recommendation to affect the study was that the questionnaires were not suitable to be administered over the phone; therefore the questionnaires were

only administered by post to those people who had already taken part in the initial study and by interview or post to future recruited patients. The title was also amended to “adherence” rather than “compliance” as suggested by the Ethics committee and in the literature (218).

Inclusion criteria for sub-study

The sample were all the patients that were included in Beaumont Hospital “Aspirin effectiveness study in patients with stable coronary artery disease”, who were willing and able to sign the consent form and complete the study questionnaires. The total number for the sample was 189 patients, 156 had already been recruited into the national study by the time the ethics approval for the sub-study came through. A further 33 patients were then recruited into the national study and asked to take part in the sub-study at the same time. These patients were given the choice either to complete the psychological questionnaires in a face to face interview or to return the questionnaire by post. The inclusion exclusion criteria can be seen below.

Exclusion criteria-for sub-study

Patients who were unable or not willing to consent to, or complete the study questionnaires.

Measures were amalgamated with the data collected from the initial national study measuring aspirin effectiveness in patients with stable coronary artery disease-these measures were-Demographics, risk factors for coronary artery disease, medical/ surgical history, medications; self reported adherence and Thromboxane B2 ELISA assay result.

All psychological predictor measurements can be found in Appendix B.

Study setting and access

The first 156 patients were sent the information leaflet, consent form and questionnaires in the post as this is the number of patients that had already been recruited into the initial national study- “Aspirin Effectiveness in Stable Coronary Artery Disease Patients in Ireland”, recruitment for this study was still ongoing and the inclusion/exclusion criteria was as above. The subsequent 33 patients were given the questionnaire by interview in a private room in the out-patient’s department after agreeing to take part in both studies and signing the informed consent form. All patients were informed that both studies were voluntary and they were free to withdraw anytime as described in the information leaflet-(see Appendix B). Patients were reassured that their responses were confidential and would not influence their future treatment.

Study Design-

This study combined a cross-sectional, observational design along with a retrospective design. The cross sectional design was used for the initial stage of randomly selecting patients with coronary artery disease from the outpatients department, and the retrospective design was used for the patients that had already consented to the initial study but not the sub-study.

Procedure

Cross-sectional – interview

Retrospective - postal

The blood sample to measure the thromboxane level and the self reported adherence questions were measured at the same time with all patients (as the self report question was part of the national study). The psychological questionnaires were only measured at this same time point in the patients recruited after patient 156, as previously mentioned this is when we received ethical approval for the current sub - study. The first 156 patients were sent the psychological questionnaires in the post but the questionnaires have been shown to be reliable over time (219) as shown in the literature review. This was considered not to be a significant influencing factor on how patients would respond but would be analysed in the results.

Blood collection procedure

When performing platelet function studies, it is important to limit inadvertent platelet activation.

Veno-puncture can cause a degree of platelet activation. Multiple sticks and patting on the veno-puncture were avoided as per protocol.

Blood was drawn by veno-puncture using a slow drawing back of the plunger using the starstedt monovette blood collection system and a 22g needle

It was ensured that the tourniquet was not too tight or on for too long (less than 30 seconds) and released as soon as the blood flow started as recommended by the protocol, in order to avoid platelet activation.

Samples were placed at 37 degrees Celsius within thirty minutes of blood draw (min of 30 minutes and max of 60 minutes on hot block)

Note -“Arm to centrifuge time”- samples reached the centrifuge within 60mins of the blood draw.

The sample was centrifuged at 900g (900rcf) for 10 minutes.

Serum was removed from the centrifuged sample using a pipette and divided into 3 serum aliquots which were clearly labelled with the individual patient identifier number for the study.

All samples were stored at -80 degrees Celsius.

All samples were meticulously managed to ensure the integrity of the samples and correct labelling storage, tracking and delivery to RCSI (215).

Recorded variables

The following demographic and clinical variables were recorded: age, gender, living with spouse /partner, employment status, education, private health insurance, alcohol intake, smoking history, hyperlipidaemia, weight, hypertension, diabetes, family history of coronary artery disease, physical activity, history of myocardial infarction, history of coronary artery bypass grafts, history of coronary stents.

Employment is shown as a categorical variable (yes/no) by collapsing the subgroups down to the binary variable, as well as subgroup employment status in order to give a good overall picture of the responders and non-responders, although there was no significant difference between the groups, or on adherence.

Although smoking was divided into never, current, previous and cigar/pipe in the original questionnaire looking at demographic data, this was converted into a categorical variable of history of smoking or not. There was no significance in adherence between those that smoked and those that did not. Family history was also converted into a yes/no variable (although there was also an unknown option). These variables are shown as categorical for presentation purposes collapsing the above variables did not show or hide

any significant associations among the various versions of these variables and adherence.

Questionnaires

Beliefs about medicines questionnaires

The necessity-concerns framework was assessed using the BMQ. The BMQ consists of two subscales - beliefs about medicines in *general* (*BMQ-General*) and specific beliefs about medicines a person is taking themselves, (*BMQ-specific*) assesses patient's beliefs about their prescribed medication. It consists of two subscales: firstly, the specific-necessity scale assessing beliefs about the necessity of their prescribed medication for controlling their illness and maintaining their health and secondly, the concerns about the adverse consequences of taking prescribed medication are assessed using specific concerns scale (132). Patients score their degree of agreement with each statement on a five-point Likert scale ranging from 'strongly disagree' to 'strongly agree' (score range 1-5 for each question).

The beliefs about medicines *specific* is divided into two sub-scales: specific necessity scale 5-25, with 5 being the lowest possible score and 25 being the maximum score and the specific concerns scale 5-25, also, with 5 being the lowest score and 25 being the highest score. A necessity-concerns differential score was calculated by subtracting the specific concerns scale from the specific necessity scale –range -20 to +20 as described by Horne et al. (17, 132). A positive differential score indicates stronger necessity beliefs than concerns and a negative score indicates the contrary i.e. stronger concerns.

See Appendix B.

The beliefs about medicines questionnaire - (BMQ) *general* consists of eight questions with a Likert scale ranging from strongly disagree to strongly agree (scores 1-5 for each question), thus the score can range from 8-40 with a higher score indicating a more negative general view regarding medications (See Appendix B).

Brief Illness Perception questionnaire

This questionnaire is based on Levanthal's self-regulatory model of health management that describes the process by which patients respond to a perceived health threat (136). The questions relate to identity, timeline, consequences, and cause, looking at control and emotional factors showing the patient's beliefs about the perceived symptoms of the condition, its duration, and nature. Negative beliefs surrounding the illness and treatment may lead to non-adherence to medicines (16). High scores regarding control and cure and illness understanding show positive beliefs about the controllability of the condition. This may lead to adherence to medicines (83). The *brief* illness perception questionnaire works in the same way as the illness perception questionnaire *revised*, but is much shorter and simpler and therefore more practical in the clinical setting (125).

The Illness perception questionnaire suggests patients cluster their ideas about their illness around the components above to provide a framework for patients to make sense of their symptoms, assess health risk, and direct action and coping. The source of people's perceptions of illness is diverse and

ranges from first hand experiences with a family member who may suffer from an illness, to information from their relatives and friends as well as the media. These perceptions may lie dormant until they are activated by their own illness or someone close to them (125). Each item of the Brief Illness Perception Questionnaire assesses one of the dimensions of illness perceptions as shown in Appendix B, and scores range from 1-10. The internal consistency of the score has previously been validated in patients with coronary artery disease (219).

The Patient Health Questionnaire-2 (PHQ-2)

As described in Chapter 4, Summers et al (147) advises only psychometric instruments that have been validated in the cardiac population such as the PHQ-2 should be used for depression screening.

The PHQ-2 inquires (164) about the frequency of depressed mood and anhedonia over the past two weeks (220, 221). The PHQ-2 includes the first two items of the PHQ-9 and the purpose is to screen for depression in a first step approach rather than diagnose or monitor depression. Reducing depression evaluation to two screening questions enhances routine enquiry (153), keeping to a minimum the number of items asked about a single disorder is an important factor to ensure a reasonable length for such questionnaires and it has been suggested that this may be particularly relevant for research studies where asking a few questions rather than many questions can reduce the respondent burden. A PHQ-2 score ranges from 0-6. A cut-off score of 3 is suggested by authors (153) as the optimal point for screening purposes and state that a cut point of 2 would enhance sensitivity,

whereas a cut point of 4 would improve specificity. For the purpose of this study the PHQ-2 will be analysed as a continuous variable. Patients that are considered to be particularly vulnerable at the time of consent (patients showing visible signs of stress where the procedure of consent and phlebotomy would cause further distress, assessed by experienced clinical qualified nurses and doctors) would not be included as recommended by Fulford and Howse (223) and the Beaumont Hospital Medical Ethics Committee and HSE guidelines 2014 (approval letter Appendix B).

It is recommended that unless vulnerable groups are going to benefit directly from the research they should not be specifically targeted. As the clinic is an outpatients cardiology clinic the amount of patients considered vulnerable would be minimal 1-2 and unlikely to bias the sample.

ENRICHD- ESSI social support questionnaire

As described in Chapter 5, the ENRICHD study (Enhancing Recovery In Coronary Heart Disease) was designed in response to the large amount of research showing the effects of social support on health outcomes. The questionnaire has shown good reliability and validity in cardiac patients in a later study by Vagilo et al. (204), thus the ESSI (ENRICHD Social Support Instrument) was chosen to assess social support. The majority of questions on the ESSI consider general feelings about being loved and valued rather than instrumental types of support. This assesses the theory that social support is more about patient's belief that others care about them and are available if needed, rather than actual support services and that quality rather

than quantity seems to be more important in patients with chronic disease (183, 185). The social support is measured using a Likert scale of 0-4 with a possible maximum score of 24 and possible lowest score of 0 (See Appendix B). The final question assesses whether the patient is married or living with a spouse which will be assessed in conjunction and also separately to the other measures of social support. The ESSi appears to be a valid and reliable measure of social support in patients undergoing treatment for coronary artery disease (183).

Adherence

Adherence was assessed in two ways –self-report and objective.

Self-reported adherence was assessed by asking the question: “Number of days missed in the past week for whatever reason?” with an answer range of 0-7. This question has previously been shown to be an effective measure of adherence in brief interviews (12, 222), this was looked at both dichotomously as yes/no and as a linear scale of 1-7.

Objective adherence as assessed by using thromboxane B2 ELISA with a cut-off point of $> 2.2\text{ng/ml}$ indicating non-adherence as advised by Maree et al. (217). Adherence (i.e. $<2.2\text{ng/ml}$) is indicated with the value of 1 when dichotomised for statistical purposes, with non-adherence being classified as 0 (greater than or equal to 2.2ng/ml).

Statistical Analysis

The collected data were entered into an Excel spread sheet and then checked for errors by simple inspection of the original questionnaires and the code book. The data was then imported into SPSS version 21 and combined with

the data from the original aspirin study. The data was examined using descriptive statistics and missing data was minimal (one or two questions in less than ten patients), therefore the mode for that person's other items was entered as suggested by Tabachnick and Fidell (223), missing data was cross referenced with thromboxane level to ensure there was no correlation with missing data and lack of thromboxane result, i.e. were the patients that left out questions non-responders to aspirin and likely to be non-adherent. There was no correlation seen as the patients with missing data were all responders.

Statistics were carried out on both groups separately (those that were interviewed and those that were sent the questionnaires by post) as well as one whole group to observe for any significant differences between the two groups.

Data were analysed using descriptive statistics and Pearson's correlations (for continuous variables). Logistic regression and t-tests were used to predict adherence or not to aspirin using demographic and clinical variables (binary variable: 1 < 2.2ng/ml, 0 > 2.2ng/l). T-tests were also used to assess differences in the psychological variables among those who were adherent and those that were not as determined by self-report and thromboxane effectiveness. Finally, a multivariate logistic analysis was conducted, including all significant predictors of adherence, in order to build a multivariate model that could be used to determine if these variables accounted for any potential psychological correlates of adherence. (Thromboxane was also analysed as a continuous variable - see Appendix B). Diabetes, smoking history and family history of

CAD were looked at as categorical and using Cramer's V as recommended by Pallant (224).

CHAPTER 8 - Results

Response rate

A total of 189 patients were approached to participate in the survey, and 106 (56%) provided consent and completed the questionnaires. Of those approached, a total of 156 patients were sent the questionnaires via post and 75 of these responded (48%). Patient recruitment for the national study was still ongoing at the time of ethics approval for the current study (sub-study), therefore the final 33 patients were asked to take part in both studies face to face in the cardiology outpatient clinic. When asked to complete the questionnaire face to face, 31 out of 33 (94%) of patients agreed to take part in the sub study, with most patients preferring to complete the questionnaire during their time in clinic although given the option to take the questionnaire away and return via post. Two patients took the questionnaire home from clinic with one subsequently returning the questionnaire by post.

Table A1 in Appendix A, shows the demographic differences between the postal and interview groups. The only significant difference that can be seen between the postal and interview group in the sample who were approached to participate is in the employment status (see Appendix A). The combined sample (n=106; postal and interview groups) is compared to non-responders in Table 8.1.

Table 8.1: Responders and non-responders to the questionnaire

Overall sample- Demographic	Responders (n=106)	Non- responders (n=83)	Statistic	P-value
Age (years)	63.1 (SD12.1)	67.6 (SD8.7)	t=2.96,df=185	.003**
Male Gender	81 (60%)	55 (40%)	$\chi^2 = 1.9, df=1$.168
Living with spouse/partner	76 (58%)	54 (42%)	$\chi^2 = 2.23, df=3$.52
Employed (yes)	30 (56%)	23 (43%)	$\chi^2 = 7.5, df=5$.18
Employment status				
Disability retirement	9/106 (9%)	4/83 (5%)		
Employed outside the home	30/106 (28%)	23/83 (28%)		
Homemaker	10/106 (9%)	15/83 (18%)		
Retired	49/106 (46%)	40/83 (48%)	Cramer's V=.200,df=5	.182
Unemployed	7/106 (7%)	1/83 (1%)		
Education				
Primary	29 (41%)	41 (59%)		
Secondary	59 (63%)	34 (37%)	Cramer's V =10.3,df=3,	.016*
Third level	17 (68%)	8 (32%)		
Private health insurance	38 (67%)	19 (33%)	$\chi^2 = 4.6, df=2$.097
Alcohol intake in 4wks	52 (SD 64.5)	41 (SD 58).	t=.95,df116	.340
Smoking History	71 (68%)	57 (70%)	Cramer's v =.099,df=4	.763
Hyperlipidaemia	95 (90%)	75 (90%)	Cramer's v =.085,df=2	.959
Weight (kgs)	86.4 (SD14.9)	80.9 (SD 16.4)	t=2.39,df=187	.017*
Hypertension/on anti-hypertensive medication	86 (54%)	73 (46%)	$\chi^2 = .09, df=2$.394
Diabetes	16 (50%)	16 (50%)	Cramer's v =.104,df=2	.843
Family History of CAD	41/106 (39%)	37/83 (45%)	Cramer's V=.067,df=3	.840
Moderate physical activity mean days/wk	3.31 (SD 2.67)	2.76 (SD 2.42)	t=-1.47,df=185	.142
History of Myocardial infarction	53/106 (50%)	42/83 (50.6%)	Cramer's V=.030,df=3	.982
History of CABG	16/106 (15%)	16/83 (19%)	Cramer's V=.087,df=3	.697
History of Coronary artery stents	67/106 (63%)	46/83 (55%)	Cramer's V=.110,df=3	.518

*=p<.05 **=p<.01***=p<.001

χ^2 = Chi- Square, CAD= Coronary artery disease, CABG=Coronary Artery Bypass Grafts

Table 8.1 shows responders to the questionnaire were significantly younger in age, and significantly more likely to have a higher weight and higher education levels overall. No other significant differences were found.

Potential differences between postal and interview groups for responders are assessed in Table 8.2

There were no significant differences between the postal and interview groups in the sample of responders to the questionnaire, although those in the postal group were marginally more likely to be married. As no significant differences were found between the recruitment methods, the entire recruited sample will be analysed together from now on.

Table 8.2 - The demographic difference between postal and interview groups in the responders to the questionnaire only group n=106.

Questionnaire responders (n=106)	Postal (n=75)	Interview (n=31)	Statistic	P-value
Tbx effective<2.2	53/75 (71%)	17/31 (55%)	$X^2=.1.79, df=1$.180
Age (years)	64.1 (SD9.9)	60.5 (SD16.2)	$t=1.16, df=39.7$.250
Male Gender-Male	58/75 (77%)	23/31 (74%)	$X^2=.009, df=1$.920
Living with spouse/partner	59/75 (79%)	18/31 (58%)	$X^2=3.7, df=1$.054
Employment status				
Disability retirement	5/75 (7%)	4/31 (13%)	Cramer's $V=.262, df=5$.200
Employed outside home	22/75 (29%)	8/31 (26%)		
Homemaker	7/75 (9%)	3/31 (10%)		
Retired	38/75 (51%)	11/31 (35%)		
Education				
Primary	19/75 (25%)	10/31 (32%)	Cramer's $V=.174, df=3$.362
Secondary	43/75 (57%)	16/31 (52%)		
Third level	13/75 (17%)	4/31 (13%)		
Private health insurance	30/75 (40%)	8/31 (26%)	$X^2=4.0, df=2$.131
Alcohol intake in 4wks	50 (SD70)	61 (SD34)	$t=-.589, df=70$.558
Smoking History	52/75 (69%)	19/31 (61%)	Cramer's $V=.179, df=4$.492
Hyperlipidaemia	68/75 (91%)	28/31 (90%)	Cramer's $V=.164, df=2$.241
Weight mean (kgs)	87 (SD14)	85 (SD17)	$T=.676, df=104$.501
Hypertensive/on anti-hypertensive medication	62/75 (83%)	24/31 (77%)	Cramer's $v=.155, df=2$.280
Diabetes	11/75 (15%)	5/31 (20%)	Cramer's $V=.269, df=5$.177
Family history of CAD	27/75 (36%)	14/31 (45%)	Cramer's $V=.258, df=3$.071
Moderate physical activity mean days/wk	3.5 (SD2.6)	2.6 (SD2.5)	$t=1.58, df=103$.117
History of Myocardial infarction	38/75 (51%)	15/31 (48%)	Cramer's $V=.165, df=3$.408
History of CABG	9/75 (12%)	7/31 (23%)	Cramer's $V=.220, df=3$.163
History of coronary stents	49/75 (65%)	18/31 (58%)	Cramer's $V=.227, df=3$.142

*=p<.05 **=p<.01***=p<.001

χ^2 = Chi- Square, CAD= Coronary artery disease, CABG=Coronary Artery Bypass Grafts

Adherence

To investigate whether demographic or clinical factors were associated with thromboxane effectiveness, these data were stratified in Table 8.3.

There was no significant difference between responders to the questionnaire and non-responders to the questionnaire in terms of thromboxane effectiveness/adherence-70/106 (66%) of responders to the questionnaire

were adherent compared to 61/83 (74%) of non-responders to the questionnaire- $X^2=.891$, $df=1$, $p=.345$.

Table 8.3 shows the relationship between the demographic data and thromboxane effectiveness

DEMOGRAPHIC	Adherent Tbx<2.2	Non-adherent Tbx>2.2	Statistic result	TxB2 effective p value
Mean Age (years)	64.4 (SD12.3)	60.4 (SD11.4)	$t=-1.61$, $df=104$.109
Sex – Males	46/70 (66%)	35/36 (97%)	$X^2= 11.4$, $df=1$.001**
living with spouse/partner	45/70 (64%)	32/36 (89%)	$X^2=6.0$, $df=1$.014*
Employment status				
Disability	4/70 (6%)	5/36 (14%)	Cramer's $V=2.62$, $df=5$.220
Employed	17/70 (24%)	1/36 (3%)		
Homemaker	9/70 (13%)	1/36 (3%)		
Retired	35/70 (50%)	14/36 (39%)		
Unemployed	4/70 (6%)	3/36 (8%)		
Education				
Primary	20/70 (29%)	9/36 (25%)	Cramer's $V=3.66$, $df=3$.290
Secondary	41/70 (59%)	18/36 (50%)		
Third level	8/70 (11%)	9/36 (25%)		
Private health insurance	29/70 (41%)	9/36 (25%)	$X^2=3.5$, $df=2$.173
Alcohol units in 4wks(mean)	30 (SD26)	83 (SD86)	$t=3.33$, $df=33$.002**
Smoking history	45/70 (66%)	26/36 72%)	Cramer's $V=.222$, $df=4$.266
Weight (mean kgs)	82.5 (SD13.6)	93.9 (SD14.6)	$t=3.89$, $df=66$.001***
Hyperlipidaemia	63/70 (90%)	33/36 (92%)	Cramer's $V=.076$, $df=2$.737
% Hypertensive/on anti-hypertensive medication	54/70 (77%)	32/36 (89%)	Cramer's $V=$, $df=2$.312
% Diabetes	11/70 (16%)	5/36 (14%)	Cramer's $V=.239$, $df=5$.299
Family history CAD	28/70 (40%)	13/36 (36%)	Cramer's $V=.087$, $df=3$.848
Moderate physical activity mean days/wk	3.42 (SD2.63)	3.11 (SD2.76)	$t=.561$, $df=103$.576
History of myocardial infarction	35/70 (50%)	18/36 (50%)	Cramer's $V=.167$, $df=3$.396
History of CABG	9/70 (13%)	7/36 (19%)	Cramer's $V=.189$, $df=3$.286
History of coronary stents	43/70 (61%)	24/36 (67%)	Cramer's $V=.117$, $df=3$.691

*= $p<.05$ **= $p<.01$ ***= $p<.001$

χ^2 = Chi- Square, CAD= Coronary artery disease, CABG=Coronary Artery Bypass Grafts

Table 8.3 shows there were significant relationships between male gender, higher weight and alcohol intake as well as living with spouse/partner and response to thromboxane showing aspirin effectiveness.

The X^2 value for self reported adherence and thromboxane adherence is $X^2=.239$, $df=1$, $p=.62$.

Five of the thirty six non-responders to aspirin therapy admitted to missing at least one dose in the previous week when asked directly regarding adherence at the time of blood draw. Six of the responders to aspirin therapy admitted to missing a dose in the last week.

TABLE-8.4-The association between self –reported adherence and adherence measured with thromboxane

Adherence measure	Adherent	Non-adherent	statistic	p-value
Thromboxane	70/106(66%)	36/106(34%)	Cramer's $V=.080$, $df=1$.409
Self reported	94/106(89.5%)	11/106(10.5%)		

There was no significant correlation between self-reported non-adherence and non-adherence measured by thromboxane B2, in the responders to the questionnaire. Rejecting the hypothesis that self-reported non-adherence would correlate with non-adherence measured by thromboxane (although there was a significant correlation found when looking at the whole Beaumont sample of 189-Table A4). The demographic differences between the adherence measures are shown in Appendix A6

Correlations between the psychological variables.

The correlations among the psychosocial measures are shown in Table: 8.5

Table 8.5 Psychological measures-Correlation matrix of psychological variables

	Social support ESSI Tot	Beliefs about Medicines BMQ spec	Beliefs about Medicines BMQ gen	BIPQ-1, how the illness effects your life	BIPQ-2, how long the illness will last	BIPQ-3, how much control you have over your illness	BIPQ-4,how much you think your treatment can help your illness	BIPQ-5,how much do you experience symptoms from your illness	BIPQ-6,how concerned are you about your illness	BIPQ-7,how well you feel you understand your illness	BIPQ-8,how much does your illness affect you emotionally
PHQ-2, total depressive symptoms	-.36**	-.30**	.35**	-0.3	.31*	.21*	.18	.23*	.40**	.19	.68**
ESSI Tot		-.10	-.21*	-.10	.01	-.19	-.26*	-.12	-.32**	-.19	-.41**
BMQ specific			-.58**	-.11	-.04	-.24*	.33**	.39	-.12	-.32**	-.32**
BMQ general				.37**	.00	.38**	.33**	.39**	.39**	.26**	.21*
BIPQ-1					.17	.20*	.07	.66**	.49**	.07	.47**
BIPQ-2						.24	-.05	.19	.13	.00	.11
BIPQ-3							.11	.34**	.32**	.32**	.38**
BIPQ-4								.09	.18	.44**	.26**
BIPQ-5									.45**	.00	.46**
BIPQ-6										.21*	.54**
BIPQ-7											.20

PHQ-patient health questionnaire, BMQ-beliefs about medicine, ESSI-social support, BIPQ-beliefs about illness *= $p < .05$ **= $p < .01$

Significant positive correlations were shown between depressive symptoms and negative general beliefs about medicine, the perception of how long the illness is going to last, perceived control over the illness, symptoms, concerns over the illness and how it affects the subject emotionally. There was a large correlation between depressive symptoms and how the illness affects the patients emotionally as expected.

There was a strong positive correlation between concerns over the illness and how the illness affects the subject emotionally.

Significant negative correlations were shown between depression and social support, and positive beliefs about medicine specific.

There was also a negative correlation between social support and negative beliefs about medicines in general, and perception of the treatment helping.

There was a strong negative correlation between social support and how the illness affects the subject emotionally and also concerns over the illness, the more social support the less emotional effects and concerns over the illness.

TABLE 8.6 - The relationship between self reported adherence and the psychological questionnaires (n=106)

	Self reported adherence (Mean, SD)	Non-adherence (Mean, SD)	T-test (t-value)	P-value
Social support ESSI	19.5(6.1)	21.1(4.0)	-.865,df103	0.389
PHQ-2 Total Depressive symptoms	1.10(1.64)	.55(1.03)	1.081,df103	0.282
Beliefs about Medicines BMQ (specific)	33.6(5.8)	33.6(3.6)	-.022,df103	0.982
Beliefs about Medicines BMQ (general)	20.3(4.6)	21.8(5.6)	-.960,df103	0.339
BIPQ-1, how the illness effects your life	4.13(2.77)	4.18(2.08)	-.062,df103	0.950
BIPQ-2, how long the illness will last	9.15(2.27)	8.18(2.48)	1.321,df103	0.189
BIPQ-3, how much control you have over your illness	4.11(2.9)	2.91(1.57)	1.333df103	0.185
BIPQ-4,how much you think your treatment can help your illness	1.57(1.87)	2.00(2.19)	-7.00,df103	0.486
BIPQ-5,how much do you experience symptoms from your illness	4.15(2.80)	3.27(2.37)	.995,df103	0.322
BIPQ-6,how concerned are you about your illness	5.29(3.48)	5.18(2.96)	.096,df103	0.923
BIPQ-7,how well you feel you understand your illness	2.31(2.70)	1.27(1.84)	1.233,df103	0.221
BIPQ-8,how much does your illness affect you emotionally	3.70(3.38)	2.91(2.54)	.750,df103	0.455

There was no relationship between the psychological questionnaires and self reported adherence.

There were also no significant correlations between the psychological variables and self-reported missed doses of aspirin using Logistic Regression.

See Appendix TABLE A5

The association between the psychological predictors of adherence and thromboxane levels are reported in table 8.7

TABLE 8.7- The association between the psychological predictors of adherence and thromboxane

Questionnaire	Thromboxane adherence (mean, SD)	Non-adherence (mean, SD)	T-test	P-value
Social support ESSI total	19.3(6.2)	20.3(5.2)	.844,df104	0.401
PHQ-2 Total Depressive symptoms)	1.04(1.76)	1.00(1.21)	-.130,df104	0.896
Beliefs about Medicines (BMQ specific)	33.8(5.2)	33.0(6.4)	-.689,df104	0.492
Beliefs about Medicines (BMQ general	20.7(4.8)	20.1(4.5)	-.605,df104	0.546
BIPQ-1, how the illness effects your life, Mean (SD)	4.11(2.78)	4.11(2.58)	.006,df104	0.995
BIPQ-2, how long the illness will last, Mean (SD)	8.96(2.52)	9.08(1.97)	.261,df104	0.795
BIPQ-3, how much control you have over your illness, Mean (SD)	4.09(2.99)	3.81(2.45)	-.483,df104	0.630
BIPQ-4, how much you think your treatment can help your illness, Mean (SD)	1.69(1.73)	1.53(2.21)	-.404,df104	0.687
BIPQ-5, how much do you experience symptoms from your illness, Mean (SD)	4.21(2.98)	3.75(2.22)	-.822,df104	0.413
BIPQ-6, how concerned are you about your illness, Mean (SD)	5.06(3.30)	5.69(3.60)	.913,df104,	0.363
BIPQ-7, how well you feel you understand your illness, Mean (SD)	2.40(2.71)	1.81(2.45)	-1.10,df104	0.273
BIPQ-8, how much does your illness affect you emotionally, Mean (SD)	3.54(3.46)	3.72(2.99)	.264,df104	0.792

There was no significant relationship between the psychological questionnaires and adherence measured with thromboxane B2.

Rejecting the hypothesis, the psychological questionnaires would correlate with non-adherence measured by thromboxane.

In order to determine if any of the group differences could be masking associations, a multivariate analysis was conducted to determine the most important predictors of thromboxane response. This is shown in Table 8.8:

TABLE 8.8 Multivariate analysis of the most important clinical and demographic predictors of thromboxane response.

	Exp(B)OR's	95% C.I lower	95% C.I upper	Sig p- value
Gender male	.000	.000		.999
Living with spouse/partner	.325	.067	1.56	.161
Alcohol intake in the last 4ks mean	.979	.963	.996	.017**
Weight	.960	.921	1.00	.058

*=p<.05 **=p<.01

The above logistic regression was repeated without gender, which is shown in the appendix A8 - showing more significance in alcohol intake and weight.

Both alcohol and weight seemed to be important factors, and therefore further analysis for each psychological predictor was conducted, adjusting for alcohol and weight. The results are in Table 8.9:

TABLE 8.9- Multivariate analysis of the psychological indicators adjusting/controlling for alcohol and weight

Variable	Exp(B)OR's	95% C.I lower	95% C.I upper	P-value
Social support ESSI	0.961	0.871	1.06	.431
PHQ-2 Total Depressive symptoms	0.867	0.578	1.29	.488
Beliefs about Medicines BMQ (specific)	1.013	.913	1.12	.807
Beliefs about Medicines BMQ (general)	.902	.777	1.04	.178
BIPQ-1, how the illness effects your life	.934	.750	1.16	.539
BIPQ-2, how long the illness will last	.985	.755	1.28	.911
BIPQ-3, how much control you have over your illness	.985	.815	1.19	.878
BIPQ-4,how much you think your treatment can help your illness	1.08	.769	1.54	.631
BIPQ-5,how much do you experience symptoms from your illness	.963	.776	1.19	.730
BIPQ-6,how concerned are you about your illness	.983	.835	1.15	.832
BIPQ-7,how well you feel you understand your illness	1.104	.833	1.38	.387
BIPQ-8,how much does your illness affect you emotionally	.967	.807	1.16	.737

Again, no psychological variable predicted adherence, even while controlling for weight and alcohol using a multivariate analysis.

CHAPTER 9 – Discussion

Introduction

The current research study found no association between established psychological predictors of adherence and self reported non-adherence or objectively measured non-adherence.

This chapter will give an overview of what we know already from previous research on the psychological indicators of medication adherence. It will compare the findings from the national study and then discuss how the current sub-study results are similar to the original national study. Exploring the relationships between the clinical characteristics of the sample and adherence measured by a thromboxane level of $<2.2\text{ng/ml}$. It will then discuss the results of the psychological aspects, which have predicted adherence in previous studies but had no significant correlation in this study. Finally it will discuss the limitations and the need for more randomised clinical trials before suggestions for interventions can be recommended to improve medication adherence.

Previous research on the predictors of adherence

Several studies have shown that adherence can range between nine percent in low income countries to sixty two percent in high income countries (8, 10, 11).

As described in Chapter 1, cardiovascular disease remains the single largest cause of death in Ireland (1). Low socio-economic status, lack of social support, stress at work and in family life, depression, anxiety and type D personality all contribute to the risk and poorer prognosis of CVD (3). These risk factors have also shown to act as barriers to effective treatment

adherence including medication adherence (4). Osterberg et al. (14) points out the importance of considering the psychological reasons for non-adherence and to avoid labelling patients, which may stigmatise them in their future relationship with health care providers.

Previous literature also supports the theory that the optimal threshold for adherence between medications is quite different due to pharmacokinetic and pharmacodynamic properties depending on the clinical setting. Immediately post coronary stenting the optimal threshold may be as high as 100%, whereas in other settings where patients are of low cardiovascular risk requiring statins, a clinically relevant threshold for defining adherence may be lower (23). Kronish and Ye (18) suggest that increasing our understanding of the optimal cut off point for adherence in cardiovascular medications may lead to a more precise understanding of the problem and the populations that adherence interventions should be targeted towards.

It is estimated that there are 194,000 deaths and a cost of 1.25 billion a year due to medication non-adherence (24), so these figures indicate the potential improving medication adherence could have on improving health outcomes. When we look at the literature, most studies as shown in Tables 1, 2, 3 and 4 have used self reported adherence which has been shown to overestimate adherence by 10-20% compared to objective measures (39), thus the savings could be more if we find effective ways of improving adherence.

Conflicting findings

The literature on adherence is inconsistent and often has conflicting findings, possibly due to the nature of non-adherence being complex and multifactorial (43). The literature on the Beliefs about Medicines Questionnaire (BMQ) claims peoples beliefs about medicines remain stable over time (17), but it is also claimed that patients' conditions and circumstances have been shown to have an effect on adherence for example socio-demographic status, lifestyle including alcohol intake, disease severity and patient education (21, 68, 69). Previous consistent predictors have been beliefs about medicines, beliefs about illness, depression and social support (21, 71, 72) but these psychological predictors are also interdependent and can be influenced by the patient's circumstances at the time. Research has suggested that the severity of the patient's condition can also be a barrier to adherence, particularly if this is causing depression

We can see from the previous study carried out by O'Carroll and colleagues (13) funded by the Scottish government looking at secondary prevention of stroke with aspirin therapy, that this study highlighted the importance of a valid and reliable tool to measure adherence, as patients generally over report medication adherence in a sociably desirable way. Unfortunately they found their measure of adherence using urine measurements of salicylate levels to be unreliable therefore this measure could not be used in their final analysis. A previous study looking at the role of weight and enteric coating on aspirin response in coronary artery disease patients showed the Thromboxane B2

ELISA assay to be a reliable measure in detecting aspirin adherence as several other studies (58, 214, 217)

Beliefs about medicines

The literature also suggests that the clinical nurse specialist plays an important role in identifying patients that are non-adherent in the clinical setting. Horne et al. (2) have demonstrated that beliefs about medicines were more powerful predictors of self-reported adherence than the clinical and socio-demographic factors in patients with coronary artery disease.

Measurement of adherence if asked in a non-accusatory way by a research nurse have also correlated with 50% of the non-adherence measured with thromboxane B2 ELISA in a study carried out in our own institution previously (12).

A review of the literature on beliefs about medicines showed mainly self reported adherence measures, and only two studies that used an objective measure of adherence- the UMPIRE study which included high risk cardiovascular disease patients (but not established coronary artery disease therefore not included in the table) where blood pressure and cholesterol levels in patients that were randomised to the “polypill” were monitored. There were significant but small reductions in systolic blood pressure and cholesterol levels. The Bermingham (104) study found a correlation with the Beliefs about Medicines Questionnaire and self reported adherence but not cholesterol level goal achievement. Thus there were no studies that used a reliable objective measure in patients with coronary artery disease.

As this is the first study to use the objective measure of thromboxane, it is possible this is why there were no correlations found with the Beliefs about Medicines Questionnaire. It is also of note that as patients were recruited in clinic by some-one that may not be viewed as completely independent to the clinical team, patients may have responded in a socially desirable way or worried how their answered might be perceived. There is also the possibility that the study wasn't powered sufficiently to take this bias into consideration.

Beliefs about illness

The beliefs about illness questionnaire has not been without criticism (225), Van Out et al. (225) describes how in a cross-sectional observational study they found that patients had a number of problems completing the questionnaire and call into question the construct validity of this measure; Broadbent et al. (2011) disputes this study suggesting translational problems (226), but French et al. (2011) argue that it does not have robust psychometrics (135).

A previous study by Petrie et al. (106) found that whether patients were sent the questionnaire in the post or recruited in the clinical area, was unlikely to have on the effect on patient's perceptions of their illness. Byrne et al.'s study (100) looked at 1611 patients with established coronary heart disease; this study was designed to evaluate the use of the illness perception and medication beliefs in predicting secondary prevention behaviour among patients with coronary artery disease. Patients over 80 years old were excluded, and patients were recruited from GP practices so were likely to be less acute than patients recruited from a hospital. They also found that beliefs

about medicines were only moderately related to self-reported non-adherence explaining only seven percent of the variance.

Aalto et al. (128) found that older patients perceived less symptoms of coronary artery disease and shorter expected timeline of the duration of the illness. It has been argued that older patients may have developed more effective coping skills and self-efficacy than the younger patients. They suggest that if we modify patients' perceptions on self-efficacy and resource support, this may have a positive effect on medication and behavioural adherence, thus medical outcomes. Table 2 shows only two studies that used an objective measure of adherence and these studies were not predictive of other health outcomes. Brandes and Mullen (109) have concluded from their meta-analysis that the Brief Illness Perception Questionnaire (BIPQ) is weak in predicting adherence and may be more predictive of adherence in acute patients. Therefore the results from the current study of patients who are stable with coronary artery disease showing no correlation with the Brief Illness Perception Questionnaire (BIPQ) may not be entirely surprising. It is also possible that the full version of the illness perception questionnaire may have shown correlations but as discussed in chapter 3, the brief version has been shown to be valid and reliable and more user and patient friendly particularly when used with multiple questionnaires.

Depression

Several studies have shown a direct relationship between depression and non-adherence to cardiac medications and as well as a higher prevalence of

depression in cardiovascular patients (214). It has also been shown that there is a higher risk of cardiovascular disease in patients that suffer with depression than patients that do not. Positive beliefs and expectations are known to be essential for patients to adhere to a healthy lifestyle including adhering to prescribed medications. Only four studies in Table 3 show the relationship between depression and medication adherence in coronary artery disease patients. Two of these studies used self-reported measures of adherence (160,176) and two used electronic monitoring devices (173,175) where the patients were aware their medication adherence was being monitored and in a small group of patients (65-patients) that didn't include patients over 75 yrs. This reduces the generalisability of the findings.

Doyle et al. (227) found in their study of symptoms in patients with acute coronary syndrome (ACS), that people with symptoms of fatigue-sadness consistently predict prognosis whereas anhedonia and depressive cognitives did not. They suggest some aspects of depression are more cardiotoxic than others and it's possible these were not measured in the current study using the brief depressive symptoms measure (PHQ-2).

This is the first study to use the objective measure of thromboxane and although the patients knew their aspirin effectiveness was being measured they may not have realised non-adherence might also be inferred, thus this may be the reason why no correlation was found. Patients who know they are signing up for studies that will monitor adherence will generally behave differently if they know they are being monitored, "Hawthorne effect". This is also seen with patients in clinical trials as mentioned previously.

Social support

Previous studies have shown the strong link between social support and health outcomes in cardiovascular disease patients. Aggarwal et al. (201) found a significant correlation between patients who reported planning or having a paid caregiver and a 40% increase in medication adherence.

Cardiac patients often rely on reminders from family members to carry out daily tasks such as medication taking and the theory is that paid caregivers are more accountable and trained than informal caregivers. There does appear to be more research showing that the presence of a spouse or partner increases medication adherence as well as health outcomes (202,205). The literature suggests that there is a two way link between social support and adherence in that the adherent patient tends to receive more support and vice versa. There is also the strong relationship between social support and depression, where patients that suffer from depression tend to isolate themselves and isolation tends to increase depression and can in turn lead to neglect of daily self-care activities including medication adherence.

It can be seen from table 4 that there appears to be a lack of research on social support and medication adherence in coronary artery disease patients, with no studies using a direct measure of medication adherence with other important variables such as depression and beliefs about illness and medication. There was no correlation found between social support and thromboxane, possibly due to this being the first study to use this objective measure in coronary artery disease patients. There was a significant correlation found between patients that were married or living with a spouse and adherence ($p=0.01$). There was no remaining significance after

multivariate analysis of the most important clinical and demographic predictors; gender, weight and alcohol intake-Table 8.8. This is likely due to higher number of males and married/living with spouse patients in the sample population and also found in previous studies.

A comparison of results from national study and sub-study

The objective of the national study was to measure aspirin effectiveness in stable coronary artery disease using the thromboxane B2 ELISA assay in 8 different centres in Ireland, there were 700 patients recruited in total (219). The results from this study shows good comparability to other studies with regard to the types of patients recruited, therefore should have a degree of generalisability.

For the current sub-study, there were similar representations of patients by age, weight, gender, diabetes, hypertension, hyperlipidaemia, family and smoking history, and alcohol intake as shown in table 8.1. The response rate was 56% n= 106 out of a sample frame of 189 patients in Beaumont which is acceptable and expected when using postal questionnaires (138, 228). The mean age of patients in total Beaumont sample was 65 years, whereas the mean age in the responders to the questionnaire group was slightly lower at 63 years. There was a higher percentage of non-responders to aspirin in the current sub-study 34% compared to the national study 20%, this may be due to the areas where the patients were recruited i.e. patients recruited in Beaumont were mainly from the out patients department, 92% compared with other sites where patients were recruited in cardiac rehabilitation (8% of Beaumont hospital patients were recruited from cardiac rehabilitation, 100%

had an effective response to aspirin). The remainder of the patients were recruited from out-patients. Patients are more likely to be adherent due to a more recent cardiac event and closer monitoring as well as showing signs of adherence by attending cardiac rehabilitation, as shown in previous studies (229).

The findings from the national study were that patients that were overweight and had a higher alcohol intake were more likely to have an ineffective response to low a dose aspirin of 75mgs (215). The findings in the sub-study supported these conclusions as with similar studies recently (13). There was a significant negative correlation between alcohol consumption and aspirin effectiveness as with the larger national study. This is consistent with the literature that shows significant correlations between high alcohol intake and lack of medication adherence (230). This has been previously shown in studies looking at adherence to HIV medication (230), but the interventions used to increase adherence in this cohort of patients failed to deliver significant improvements (231). The randomised clinical trial that was carried out by Somet et al. (230) to enhance antiretroviral medication in patients with a history of alcohol problems did not show significant improvements using a targeted intervention on adherence to medication, but they do suggest that addressing alcohol problems may lead to an increase in medication adherence as this was the main predictor of non-adherence (236). They found that patients that managed to abstain from alcohol increased their adherence therefore addressing the issue of high alcohol consumption is likely to increase adherence in other groups of patients, including patients with

coronary artery disease. Several studies have been completed on patients in Ireland that suggest 25% of all admissions to hospital are alcohol related (232). Addressing high alcohol consumption is likely to have a beneficial effect on adherent behaviours including medication adherence. There was no correlation between alcohol consumption and self reported adherence or the psychological variables, possibly due to patients responding in a socially desirable way. It is interesting that patients admit to their high alcohol intake, possibly due to an accepting alcohol culture that can be seen in practice and from the above literature.

The current sub-study found responders to the questionnaire were found to be significantly younger in age with a significantly greater likelihood of having a higher weight and higher level of education. There were no significant differences between the patients that responded by interview questionnaire or by post, in either the demographic data or the psychological questionnaires, although the responders by post were marginally more likely to be currently living with a partner or spouse.

Strategies suggested by the Department of Psychiatry and Behavioural Medicine from the University of Florida, advise on the importance of the provider–patient relationship. They advise on establishing a trusting relationship with the patient, assessing patients' understanding of the disease state and treatment, involving the patients in setting treatment goals, while assessing the patient's readiness to adhere to a plan. They suggest tailoring regimens to fit within a daily routine, providing written instructions (233). This

has been previously recommended by researchers suggesting a multidisciplinary approach is the way forward (234).

This is the approach that can be observed currently in the outpatients department and cardiac rehabilitation where the experienced health care providers understand the importance of adherence and take the time to reinforce the necessity of anti-platelet therapy. The success of the experienced multidisciplinary approach can be seen from the 8% of patients that were recruited from cardiac rehabilitation, where there was a 100% response rate to aspirin therapy.

Thromboxane level as an indicator of adherence

The results from the national study and the sub-study are consistent with previous findings looking at aspirin resistance or lack of adherence (12, 14) showing that between 20-35% of patients are inadequately inhibited.

Self reported adherence was assessed in the initial national study "Aspirin effectiveness in stable coronary artery disease", whereby patients were asked if they had missed their aspirin dose in the last week either intentionally or unintentionally (235). There is conflicting evidence in the literature which supports this as an accurate measure of adherence due to socially desirable responding (13), but it is expected that if patients admit to not taking their aspirin that this should correlate with the measure of thromboxane (12).

Grove et al. (236) found in their comparison of platelet function tests and thromboxane metabolites to evaluate aspirin response that conclusions based on platelet function testing strongly depend on the assay used. They found that serum thromboxane and the VerifyNow aspirin test were the most reliable

assays. Blais et al. (237) suggest that some of the variability in the reported “resistance to aspirin” is unrelated to aspirin intake, but more likely to do with the limitations of the assays to detect aspirin or due to the variability of platelet activity independent of aspirin mediated cyclooxygenase-1 inhibition.

Frelinger’s (238) study supports the above findings stating that the term aspirin resistance is inappropriate for the same reasons, although suggests a cut-off point of $< 3.1\text{ng/ml}$ rather than $< 2.2\text{ng/ml}$, whereas Seidel (239) suggests a serum thromboxane level of $< 2\text{ng/mg}$ reflects aspirin induced inhibition with high sensitivity. Cattaneo (65) states that sub optimal response to aspirin as determined by serum thromboxane is rare and in most cases caused by poor adherence. Overall, it seems that $< 2.2\text{ng/ml}$ is an optimal threshold, and this is what was used in the present study.

This measure of aspirin effectiveness on thromboxane level appears to be the most reliable from looking at the literature (238) i.e. compared with urine salicylic acid which was used in a similar study (13) and was not a reliable indicator.

The results from the Beaumont Hospital cohort (189 patients) showed a significant direct correlation between self reported missed days and lack of response to aspirin using the binary variable of 2.2ng/l as suggested by Maree et al. (217). Although the correlation wasn’t as strong as one would expect, this was thought possibly due to confounding variables, such as hyperlipidaemia or hyperglycaemia, found to have an effect on platelet aggregation in previous studies (14, 240), which the authors suggest may have an effect on the aspirin response. However, there was no significant correlation between patients with hyperlipidaemia and diabetes and an

ineffective response to aspirin therapy that would suggest the presence of these conditions would have a confounding effect. It should also be remembered, that emotional stress has been shown to increase platelet aggregation (241), although this was not directly measured in the current study, there were no correlations found between the psychological variables and thromboxane effectiveness that would suggest this had an effect on thromboxane inhibition.

The patients may also be responding in a way that is socially desirable. As the information was being taken by a nurse who was not completely independent from the medical team there is the possibility that patients were not completely reassured that their information regarding non-adherence would be completely confidential (13), fearing being labelled as non-compliant or non-adherent in the future (15). This is also a possible reason for not seeing a correlation in self-reported non-adherence and non-response measured by thromboxane.

Although there are substantial improvements in the platelet function assays available, there still remains uncertainty surrounding how best to use the available assays and insufficient evidence to support adjusting anti-platelet therapy that will improve clinical outcomes (8, 65).

Cattaneo (59) states that two important issues should be taken into consideration when measuring platelet function in Vitro in patients on treatment with anti-platelet agents: the specificity of the laboratory tests for the

platelet activation pathway targeted by the drug and whether or not the laboratory test is performed both before and after administration of the drug. Due to the risk involved in stopping aspirin therapy in cardiovascular patients for the purpose of this study thromboxane B2 was only measured after ingestion. It could also be argued that clinically the therapeutic effect after prescription is the most important measure particularly in the acute situation, post-acute coronary syndrome or pre-percutaneous coronary intervention (PCI).

Overview of the Psychological variables in the current study

There was no significant correlation between the psychological variables and thromboxane level either as a binary variable (or as a continuous variable – see Appendix B). This raises the question whether the psychological variables are good predictors of adherence in a random sample which previous substantial research including systematic reviews, have shown they do. Findings from the Beaumont Hospital sub-study show some support for self-reported non-adherence where there was a significant negative correlation with thromboxane response when looking at the whole sample frame of 189 patients $r = -0.162$. Whereas the correlation from the responders to the questionnaire group was $r = -0.080$. It is possible, that if the response to the psychological questionnaires were higher, the study would have more power to see correlations with non-adherence with both self-report and thromboxane.

The literature in previous studies has found significant correlations between psychological indicators and medication adherence therefore it is surprising that there were no significant correlations in this current sub-study. As patients in the present study were recruited from the precursor study, patients suffering with extreme depression were less likely to be overly represented, due to practical and ethical requirements (48). It is also possible that patients with more severe depression may be less likely to attend for their outpatients' appointment. A recent meta-analysis of studies looking at the association of depression following myocardial infarction and cardiovascular events, showed forty percent of patients had major or elevated symptoms of depression (141). The authors suggest that some studies may over represent depression due to the oversampling of patients with depression. This may explain the lack of associations found with depression and adherence in the current sample.

Recent studies suggest, that in most cases non-adherence is intentional and due to perceptual barriers (51, 242). Researchers point out that the common sense model does not take intention into account, but the theory of planned behaviour does, and this may be superior in predicting adherence. Here again the research and evidence is conflicting. Sniehotta et al. (91) state that the theory of planned behaviour is no longer a plausible theory of behaviour change, and social cognitive models seem to be most predictive in the young and fit who are not representative of the population where behaviour change is most needed. DiMatteo and colleagues (112) suggests mental representations may be more appropriately measured via interviews.

Brandes and Mullen (109) point out that there is no “gold standard” for measuring mental representations or adherence and this could account for variations across studies confounding the results and findings. The authors conclude from their research that the relationships between different mental representations of the common sense model and adherence are very weak ranging from -0.02 to 0.12 and thus may not be the most appropriate model to use in predictive studies of adherence, although they acknowledge the Common Sense model may predict adherence in acute patients.

There was a strong inverse correlation between depression score and perception of social support as seen in previous studies (221). There was a significant direct positive correlation between depression and the length of time the patients felt their illness would last; more symptoms; and the more concerned they were about their illness (243). The higher the depression score the more the illness affected them emotionally but also the more they felt they had control over their illness. The higher the depression score the more negative in general regarding medications, similar to other recent studies (13). In general the more strongly the person felt about their illness or their medications the higher they scored on the depression scale which is similar to previous research (3). Therefore, the correlations between depression and the other psychological constructs were largely as expected, yet depression still did not predict thromboxane level. It is possible that using diagnostic interviews would demonstrate an association with thromboxane, and future research may assess this.

There have been recent discussions on the reliability and validity of shortened versions of psychological questionnaires (244) suggesting that they may be practical from a clinical point of view but not as reliable or valid from a psychometric point of view. Longer questionnaires tend to ask the same question in different ways adding to their validity and reliability, but measurement precision may be impaired considerably without the investigators realising (244, 245).

Interventions to promote adherence

Zimmerer et al. (2009) (246) describes how a Cochrane review showed only 5 out of 21 randomized and controlled studies concerning the improvement of adherence demonstrated significant success. However, half of the studies displayed methodological errors that weakened the statistical detection of improvement because of the low numbers of patients.

Electronic methods for compiling drug dosing histories are now the recognised standard for quantifying adherence advised by some authors (247) suggesting that the frequency of inadequate adherence is usually underestimated by pre-electronic methods. With some researchers suggesting that in the near future, one could imagine that medication adherence data over an entire therapy plan would be available as soon as the electronic wires are activated, so that a failure to take medication could be detected immediately and intervention could be taken if appropriate.

Others suggest the need for further study and dissemination of findings regarding evidence-based adherence assessment and interventions (248).

Recent recommendations from authors in the United States suggest a translational research approach (249, 250) whereby a point of care device will show the effectiveness of aspirin and other anti-platelet medication at the bedside to determine effectiveness regardless of the reason for lack of effectiveness. This will not be possible until there is consensus on the gold standard for measuring aspirin effectiveness at the bedside that proves to be cost effective on patient clinical outcomes (65). The Fifth Joint Task Force suggests that once acute emotional triggers and their mechanisms of action are understood and patients who are at risk are identified, strategies can be drawn up to prevent or minimize the risk to these patients. They acknowledge that it is difficult to speculate on the types of interventions and give examples of prophylactic therapies for high risk populations, anger or stress management, prescribing B-adrenergic blocking agents or avoiding the known triggers (4). Current recommendations and guidelines from the Fifth Joint Task Force states 'evidence suggests that reducing dosage demands is the most effective single approach to enhancing medication adherence.'

Several studies have shown that the most effective time for intervention for education regarding healthy lifestyle and adherence is immediately post an acute coronary event. This is likely to be due to firstly the knowledge that medication has saved the patient's life and trust in the treating health care providers, but also due to the support and environment that promote patients' adherence. It would appear from the current literature that if the support and encouragement is continued post discharge as with cardiac rehabilitation patients, this can increase medication adherence as well as adherence to a more healthy lifestyle in general, like diet and exercise.

Gaps in the evidence

The Fifth Joint Task Force (4) has acknowledged that there are major gaps in the evidence. They state that there is limited evidence about which interventions are the most effective and in whom (e.g. young–old, male–female, high–low socio-economic status) while also suggesting that reducing the amount of medications dosages such as using the ‘polypill’ requires further evaluation before it can be judged suitable for use in routine care (4). Meanwhile the Agency for Healthcare Research and Quality in the United States has recently published a report (251) where their aim is to close the quality gap in healthcare by improving medication adherence interventions and their effectiveness. They found the least evidence for interventions for Myocardial Infarction (MI), only one study where there was an insignificant result from an education and behavioural intervention, suggesting low strength of evidence in the benefit of interventions in this group of patients. Thus, pointing out the need for further research in this cohort of patients in the future.

They state that there is no “silver bullet” to improve medication adherence but it is typically the result of patient, provider and policy factors.

Further research is required using psychological questionnaires and objective measures of adherence.

Implications for practice

This study would support the use of reliable assays, such as the ELISA thromboxane B2 assay, in identifying patients that may be non-adherent and

addressing the reasons why, at the time, in a non-judgemental way. It is important that this is acceptable to the patients and the development of more patient friendly point of care assays, would be an advantage.

The World Health Organisation (WHO) states that: “Without a system that addresses the determinants of adherence, advances in biomedical technology will fail to realize their potential to reduce the burden of chronic illness”(45). It is recommended by the WHO that non-adherence is most effectively solved by individualised interventions addressing the multiple factors affecting adherence which include; socio-economic factors such as unemployment, lack of health insurance and limited social support networks.

We can see from the literature review above the importance of the different types of support including practical and social on medication adherence. It is also noted that information in itself is not sufficient to promote change but motivation, and behavioural skills are also critical determinants (3). This report by the WHO recommends self-management programs that provide both supportive and educational coaching interventions as multiple studies have associated coaching with improved health behaviours (252). The report also highlights the association between non-adherence and lack of health literacy, motivation and self efficacy in one’s ability to manage one’s condition; this can be explored with the questions included in the illness perception questionnaire and the beliefs about medicines questionnaire. Researchers from the COPE study (202) suggest that healthcare providers use the mnemonic COPE to assist them in using the four significant coaching concepts; connectedness

and collaboration, open ended questions, positive attitude and encouragement and support which have been shown to improve medication adherence.

The WHO advises that dealing with the factors above as well as addressing complex medication regimens and side effects, will enhance patient motivation and behavioural skills which are crucial in improving medication adherence. The 2010 Patient protection and Affordable Care Act (ACA) for healthcare reform provides financial incentives for health coaching where health plans will include expenditures for interventions that increase wellness and promote health (253). Dulmen (197) found in their review of interventions to medical treatments that interventions based on reminders and incentives can be successful in improving patient adherence and reflect the behavioural theories that show human behaviour depends on stimuli or cues that produce certain responses or rewards that reinforce behaviour. Reminders can act as cues or stimuli and incentives can act as rewards, which may maintain the behaviour after sufficient repetition. The authors note however that reminders to take medication can be less amenable than other forms of behavioural change and this is a question for future research.

Dulmen's (86) research re-enforces what Leventhal et al. (136) has previously shown, that not only do patients need to be adequately informed and believe in the message, but also believe in the messenger, which is helped by the healthcare professional having adequate training, empathy, friendliness, interest and concern (197). This is echoed by Zolnieriek and DiMateo's (254)

meta-analysis looking at physician communication and patient adherence to treatment, where they found a nineteen percent higher risk of non-adherence in patients whose physician communicated poorly, than those whose physician communicated well (the odds of a patient adhering were 2.16 times better if the physician is a good communicator $P<.001$) and training physicians in communication skills improved patient adherence by twelve percent. The authors argue that this figure is quite impressive when compared to medical interventions such as Tamoxifen in the prevention of breast cancer (.04%), plavix for reducing risks of cardiac events (.04%), and low dose warfarin preventing blood clots (15) (75).

Recent studies advise that because of the potential impact on patient outcomes, there is a pressing need to improve not only on patient anti-platelet adherence but also on provider anti-platelet therapy adherence management in cardiovascular disease (115).

Implications for future research

The previous research appears to be convincing supporting serum thromboxane B2 ELISA level of 2.2ng/l as a measure of effectiveness and/or a measure of adherence to low dose aspirin 75mgs (217). Gremmel (255) suggests that large trials with clinical outcome data are required to determine the diagnostic value of the various test systems and to define the gold standard method for assessing platelet activity, this is supported by a recent study (216). It would be an advantage if future studies incorporated other measures of adherence, such as Medication Event Monitoring Systems, pill

counts or pharmacy refill data to further validate the assay. The disadvantage of these measures has previously been discussed, i.e., they are expensive and patients may know that their behaviour is being monitored.

It would be of benefit if the study could be repeated in larger samples or other sites to determine if the findings are by chance or replicated.

Longitudinal studies would be an added advantage observing for fluctuations of adherence over time rather than a once off and examining whether there is a relationship with the psychological variables and adherence over time.

Beliefs about Medicines and illness

The NICE Medicines Adherence Guidelines suggest applying a perceptions and practicalities approach when addressing non-adherence issues (111).

Horne et al. (111) describe how non-adherence can be unintentional when the patient lacks capacity or resources, or intentional when the patient decides not to follow the recommendations which they describe as perceptual factors, where the beliefs and preferences influence whether the patient starts and continues with the prescribed medication regimen. The authors highlight how prescribing consultations are influenced by pre-existing beliefs about the illness and treatment by both prescriber and patient. This needs to be considered by healthcare providers when prescribing in order to optimise adherence and outcomes. They acknowledge the influence the economic and health care system have on adherence, but suggest that beliefs are fundamental in the prescriber/patient shared decision making process.

In this meta-analysis of studies using the Necessity Concerns Framework (Beliefs about Medicines) Horne et al. (111) found that eighty three studies

(88%) used measures of self reported adherence and eleven (11.7%) used other measures of adherence, such as pharmacy re-fill data and electronic monitoring. The association between concerns and adherence were smaller but still significant when objective measures were used and the heterogeneity around this estimate was small. The association between necessity beliefs and adherence did not differ between self report and an objective measure. They suggest that self report measures have high face validity and high specificity for non-adherence but agree that self report may be subject to recall bias and responding in a socially desirable way which may over represent adherence rates. The authors claim that this does not diminish their confidence in their findings that beliefs about medicines were related to adherence, since there is no evidence that such bias would be associated with medication beliefs. They argue that some patients with low necessity beliefs and high concerns about medicines could be expected to report higher rates of adherence in order to represent themselves positively and this pattern would increase the relationship between adherence and medication beliefs.

However it could be hypothesised that patients with more concerns would report their concerns but still remain adherent due to their concerned nature and worrying about their health i.e. Neuroticism (132). Horne et al. (111) state that the relationship between adherence and beliefs about medicines remained when objective measures were used, therefore this was not an artefact arising from the use of self reported measures. They do suggest using objective measures of adherence in future research and concentrating on conditions where there is further evidence needed. There were only four

studies in patients with Coronary Artery disease in this meta-analysis since the development of the Beliefs about Medicines Questionnaire(BMQ), with only one using the objective measure of blood pressure medication and lipid lowering therapy (103). Eighteen of the studies reviewed in this meta-analysis assessed whether beliefs about medicines could predict adherence using longitudinal or prospective designs. The authors state that the relationship was not reduced in these studies therefore they believe that medication beliefs have an influence on the self-regulation of illness and continued adherence. Using the self-regulation theory of beliefs about illness, the patient is guided by the nature, duration, cause, consequences and potential for cure or control of the illness and this is linked to whether they will adhere to their medication or not (70).

Another limitation noted in the above literature review of the BMQ (beliefs about medicine Questionnaire) was that studies outside of the United Kingdom (UK), where the disease specific modifications have mainly been developed, have reduced associations with adherence. Again, they encourage future research, which will examine the variations in the relationships that may be due to cultural differences, and differences in the health care system accessibility and economics.

Non-adherence may seem irrational particularly from the perspective of biomedicine and prescribers but non-adherence may be a common sense or informed choice response for some patients. The challenge going forward would be to assess misconceptions about illness and treatment and to avoid

prescribing unwanted treatments for the benefit of patients, prescribers and taxpayers.

Patient's beliefs about their illness and medicines specifically and in general has previously been shown to have a significant effect on behaviour and medication adherence, where the patient will carry out a cost/benefit analysis which may not always be rational as previously explained in Chapter 2 and Chapter 3. Concerns regarding medications are not limited to side effects but are also common even when they are well tolerated, patients worry about the long term effects, dependence, and cost of medications (17). More general beliefs perceiving medications as intrinsically harmful and over prescribed by doctors have also been shown in the literature (84), while package information leaflets dispensed with many prescription medicines have been shown to exacerbate concerns listing all possible side effects leaving patients confused regarding the likely risks and benefits in taking the medication.

Horne et al. (84) highlights non-adherence as a hidden problem due to patient reluctance to express doubts regarding their illness and treatment for fear of being perceived as non-compliant or untrusting in the prescriber. They suggest that the first step in promoting adherence is a "no-blame approach" that encourages an open and honest discussion to identify non-adherence and the reasons for it.

Psychological considerations

Future studies should consider personality measures i.e. type D personality, as recommended by the literature (256) and by the Fifth Joint Task Force (4). Also Uchino et al. (187) has pointed out that there may be design issues when it comes to previous studies looking at psychological measurements and health related outcomes and advises that researchers may need to model changes over time in social support. Most studies use a cross sectional design and in such studies it is assumed that the health related state is captured adequately at that point in time, whereas there may be other confounding variables.

Emilsson et al.'s (132) study, on personality traits and beliefs about medicines showed that personality traits, such as neuroticism particularly in men, was associated with lower adherence to medication. They advise that healthcare professionals be aware that a person who has a tendency towards neuroticism is likely to have barriers to taking medication grounded on concerns about potential adverse effects and the way they balance the perceived benefit (necessity) against the perceived risks (concerns). Williams et al. (256) agree that there has been considerable uncertainty regarding the role of personality factors and the risk of CVD with the resurgence of looking at personality type as a risk factor in the long term prognosis of cardiac patients. They suggest studies over the last 10 years have shown type D personality to be predictive of adverse clinical and psychological outcomes in cardiac patients. They describe how a 6-10 year follow up study of cardiac patients who were classified as type D had a fourfold mortality risk compared

with non type D patients. Type D construct has been criticised by some theorists who argue that type D personality is simply another measure of negative affectivity or neuroticism which tells us nothing new about the psychological risk factors associated with CVD. However it is the combination of negative affectivity and social isolation that is crucial (256). They advise that if type D is associated with health related behaviour, then this provides a clear target for intervention.

The European Society of Cardiology- Fifth Joint Task Force (4) suggests evidence that treatment of clinically significant depression and anxiety will improve cardiac endpoints is still inconclusive. They advise a focus on acute emotional triggers that may represent the final steps in a pathophysiological pathway that culminates in an occlusion or thrombosis, either by triggering the occlusion by vasoconstriction, or by exacerbating an already ongoing occlusion through thrombotic effects. The Task Force suggests that by studying experimental or naturalistic exposure to acute emotions, we can begin to understand the neuroendocrine/vascular/thrombotic reactions to emotions that could then be targeted for future novel and preventative therapies. The study of emotional triggers offers the possibility of improving our predictive models if we include them in future randomised clinical trials. Identifying patients that are vulnerable to emotional triggers may lead to both pathophysiological insights and improved risk stratification (4).

The questionnaires used need further validation as tools for predicting adherence in the clinical setting, preferably with other objective measures of

adherence. A recent study by Allenet et al. (37) identifies the difficulties in the various methods of measuring adherence either directly or indirectly, suggesting a crossover of the various methods that allow an idea of the adherence of the behaviour of the patient which will inform health care providers which dimension to concentrate on. The importance of adherence has been well recognised by the World Health Organisation and researchers showing that patients who adhere to their medical treatment regime are three times more likely to experience positive health outcomes (257).

As Halaris (170) advises, it is only through a multidisciplinary approach and cohesive intervention that we can succeed in unravelling the complex relationships between mental stress, inflammation, immune responses and cardiovascular disease. Uchino et al. (198) suggests a multilinear approach with a longitudinal design that incorporates social economic status may have success in documenting mechanisms responsible for the links between psychological variables and health.

Limitations and strengths

This study has several design limitations that should be noted.

The size and diversity of the sample is limited to the patients that took part in the initial study “Aspirin Effectiveness in Stable Coronary Artery Disease Patients in Ireland” that attended Beaumont Hospital and were interested in taking part in the initial study and then the sub-study. The population number and make-up limits the ability to generalize these results to the general population, although all patients were selected at random in the original

sample and are thought to be a good representation of outpatients attending Beaumont hospital with documented stable coronary artery disease.

Due to the practicalities and time constraints of the busy cardiac outpatients, the psychological questionnaires used were limited to four constructs that have previously shown correlations with adherence, although mainly self-reported. The use of a brief scale instead of a diagnostic interview for depression may have detracted from the findings. A recent study by Phillips et al. (245) suggest the BMQ should be analysed differently and researchers in the field are using suboptimal methods.

The type of medication dispenser was not recorded (blister packs or not) as Glynn et al. (258) have previously found in their systematic review of the literature on interventions to improve cardiovascular medications, this had no effect on adherence , although it may be of value in future larger studies.

The study was strengthened by using a direct assay measure, and the simultaneous measures of each construct, in a relatively large sample of patients with stable coronary heart disease. Although the response rate would have been higher if all patients were recruited by interview rather than by post. This would have added to the power of the study and may have shown more significant correlations as seen between the self-reported non-adherence and ineffective thromboxane response.

Conclusion

Although most psychological variables correlated with each other as expected, no psychological variable was associated with adherence as assessed by thromboxane B2 ELISA assay level. Researchers have consistently found testing patients' inhibition to anti-platelet therapy will detect significantly larger numbers of non-adherent patients than verbal questioning. Previous studies have also shown that a single low dose of aspirin 75mgs, will inhibit arachadonic acid measured by light transmission aggregometry (LTA) or thromboxane B2 for greater than or equal to three days. This would suggest that patients who were not adequately inhibited had been non-adherent for greater than three days (66). It therefore seems that the psychological factors measured in this study were not correlated with adherence to aspirin therapy in stable coronary artery disease patients, although further research is required to confirm this.

As with the national study, high weight and high alcohol intake had a significant correlation with non-adherence. It would appear due to the clinical time and cost constraints in the hospitals that the way forward would be to identify non-adherent patients in the clinic who may benefit from a multi-disciplinary approach with the help of pharmacists, psychologists, social workers doctors and clinical nurse specialists.

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APPENDIX A

Sample description

Table Appendix 1 shows the descriptive statistics of the sample of patients who were approached to participate.

Table Appendix A1: Demographic differences between postal and interview groups. .

DEMOGRAPHIC	TOTAL	POSTAL	INTERVIEW	Statistic. result	p-value
Questionnaire administered	189	156	33		
Response to questionnaire	106/189(56%)	75/156(48%)	31/33(94%)		
Mean age(years)	65 (SD 11)	65.9 (SD9.51)	61.3 (SD16.0)	t=1.59 df=36.9	.12
Minimum age	35	37	35	t=-.50 df=36.9	.61
Maximum age	90	90	81		
Mean weight (kgs)	84.06(SD15.85)	83.79(SD15.8)	85.36(SD16.28)		
Minimum weight (kgs)	50				
Maximum weight (kgs)	146				
Sex – Males	136/189(72%)	110/156(71%)	26/33(79%)	X ² =.000 df=1.0	1.0
living with spouse/partner(whole sample)	77/189(41%)	59/156(37%)	18/33(58.1%)		
living with spouse/partner who responded to questionnaire	77/106(72.6%)	59/75(78.7%)	18/33(58.1%)	X ² =3.7,df=1	.054
Employment status				X ² =13.8,df=5	.017
Disability	13/189(7%)	9/156(6%)	4/33(12%)		
Employed	53/189(28%)	44/156(28%)	9/33(27%)		
Homemaker	25/189(13%)	20/156(13%)	5/33(15%)		
Retired	89/189(47%)	77/156(49%)	12/33(38%)		
Unemployed	8/189(4%)	4/156(3%)	4/33(11%)		
Education				X ² =4.7,df=3	.189
Primary	70/189(37%)	58/156(37%)	12/33(36%)		
Secondary	93/189(49%)	76/156(49%)	17/33(52%)		
Third level	25/189(13%)	21/156(13%)	4/33(12%)		
Private health insurance	57/189(30%)	48/156(31%)	9/33(27%)	X ² =4.8,df2	.089

Alcohol units in 4wks mean	47.8(SD62.1)	46.38(SD65.2)	57.25(SD36.9)	t=-.649,df=116	.51
Smoking History				Cramer's V=.115 df=4	.648
Never	59/189(31%)	47/156(30%)	12/33(20%)		
Yes-Current	27/189(14%)	23/156(15%)	4/33(12%)		
Yes-Current cigars/pipe	2/189(1%)	2/156(1%)	0/33(0%)		
Yes-former quit>3mths	99/189(52%)	83/156(53%)	16/33(49%)		
Hyperlipidaemia	170/189(90%)	140/156(90%)	30/33(91%)	Cramer's V=.099,df=2	.395
% Hypertensive/on anti-hypertensive medication	162/189(86%)	132/156(85%)	30/33(91%)	X ² =1.91,df1	.38
% Diabetes	32/189(17%)	27/156(17%)	5/33(15%)	X ² =4.53,df5	.47

The only significant difference that can be seen between the postal and interview group in the sample who were approached to participate is in the employment status.

A table showing the relationship between the demographic data of the whole sample and thromboxane effectiveness is shown in table APPENDIX- table A 2

TABLE A2-Demographic data and thromboxane effectiveness.

DEMOGRAPHIC	TOTAL	Statistic.result	TxB2 effective p value
Response to questionnaire	106/189(56%)	$X^2=.89, df=1$.345
Age (years)	65 (SD11)	$t=-2.69$ $df=187$.008
Weight (kgs)	84.06(sd15.85)	$t=3.93, df=187$.000
Sex – Males Females	136/189(72%) 53/189(28%)	$X^2=5.6, df=1$.018
Living with spouse/partner (whole sample)	77/189(41%)		
Living with spouse/partner who responded to questionnaire	77/106(72.6%)	$X^2=6.0, df=1$.014
Employment status		$X^2=7.6, df=5$.177
Disability	13/189(7%)		
Employed	53/189(28%)		
Homemaker	25/189(13%)		
Retired	89/189(47%)		
Unemployed	8/189(4%)		
Education		$X^2=2.38, df=3$.497
Primary	70/189(37%)		
Secondary	93/189(49%)		
Third level	25/189(13%)		
Private health insurance	57/189(30%)	$X^2=2.93, df=2$.231
Alcohol units in 4wks		$t=2.37, df=65.5$.021
% Hypertensive/on anti-hypertensive medication	162/189(86%)	$X^2=2.82, df=2$.24
% Diabetes	32/189(17%)	$X^2=4.30, df=5$.50

The average age was 65 years. There was a significant difference between the age of the responders and the non-responders to aspirin therapy with non-responders more likely to be younger. Non-responders to aspirin were also significantly more likely to be male, with higher body weight with higher alcohol intake and less likely to be married. The majority (72%) of the sample were male, with 85% of the total sample having a diagnosis of hypertension or currently prescribed ant-hypertensive medication. The percentage of patients with a diagnosis of diabetes was 17% of the total sample. All these statistics are similar to the results from the national study of patients with stable coronary artery disease on aspirin therapy, thus there should be good generalisability to this sample (219).

Appendix Table A3 shows the difference between the postal and interview group looking at adherence (objective and self reported) looking at the whole sample of 189 patients.

TABLE A3- Adherence in postal and interview group

DEMOGRAPHIC	POSTAL	INTERVIEW	TOTAL	statistic	p-value
% Thromboxane Effective	114/156(72%)	16/33(48%)	130/189(69%)	$X^2=3.3, df=1$.069
% self reported missed days	16/156(11%)	3/33(8%)	19/189(10%)	$X^2=.000, df=1$	1.00

There was no significant difference in the thromboxane effectiveness between the responders and the non-responders using χ^2 $p=0.069$. There was no significant difference between self-reported adherence of missed days in the previous week between the postal and interview group.

69% showed an effective response of thromboxane to aspirin, with 31% showing an ineffective response of below the cut off of 2.2ng/ml (looking at the whole Beaumont sample of 189). There was a 66% effective response and 34% ineffective response in the n106 sample that responded to the questionnaire.

10% of patients reported missing at least one aspirin dose in the last week in both samples (Beaumont sample n189 and responders n106).

There was a significant biserial correlation -0.162 (sig p -value at 0.05), between self reported non-adherence (missed days in the last week) and thromboxane effectiveness $<2.2\text{ng}$, when looking at the whole sample of 189 patients.

There was a significant correlation between self-reported adherence (not missing any doses of aspirin in the last week) and thromboxane level $<2.2\text{ng}$ (OR= 0.350 , 95% confidence interval (CI) 0.134 - 0.914 , $p=0.03$) using logistic regression when looking at the whole group $n=189$. Patients that admitted non-adherence were 65% less likely to have an effective response to aspirin. There was a significant correlation between patients that admitted missing their aspirin dose in the last week and a thromboxane level $>2.2\text{ng}$ using Logistic regression.

Table A4 - Logistic Regression of missed days and Thromboxane effectiveness.

Variable	B	df	Sig.	Exp(B)	95% C.I for EXP(B)	
					Lower	Upper
Missed days	-1.051	1	.032	.350	.134	.914

There was also a significant correlation ($p=0.027$ df1) between self reported missed days in the last week and an ineffective response to aspirin using X^2 looking at the whole sample of 189 patients. Table A5 shows a table of the results using X^2 crosstabulation.

TABLE A5 - Crosstabulation of adherence

	Ineffective TxB2 response >2.2	Effective TxB2 response <2.2	Total
Missed days = No % within missed days % within TxB2effective % of Total	47 28% 82.5% 25.1%	121 72% 93.1% 64.7%	168 100% 89.8% 8.8%
Missed days =yes % within missed days % within TxB2effective % of Total	10 52.6% 17.5% 5.3%	9 47.4% 6.9 4.8%	19 100% 10.2% 10.2%
Total % within missed days % within TxB2effective % of Total	57 30.5% 100% 30.5%	130 69.5% 100% 69.5%	187 100% 100% 100%

The above table shows that ten out of nineteen patients that reported missing their daily dose of aspirin in the last week (52.6%) had an ineffective response their aspirin. Therefore for over half of the nineteen patients that reported missed days; their ineffective response could be explained by lack of adherence.

TABLE A6 - Demographic differences between the adherent patients and the non-adherent patients in the responders to the questionnaire only group N=106.

Adherence measure	Demographic	Adherent	Non-adherent	Statistic	P-value
Self report Thromboxane	Age mean (yrs)	59 (SD10)	64 (SD10)	t=1.42,df=103	.157
	Age mean (yrs)	65 (SD12)	60 (SD11)	t=-1.61,df=104	.109
Self report Thromboxane	Gender-male	70 (86%)	11 (13%)	X ² =2.3,df=1	.126
	Gender-female	46 (57%)	35 (43%)	X ² =11.4,df=1	.001
Self report Thromboxane	Married/living with spouse	67(88%)	9 (12%)	X ² =.147,df=1	.70
		45 (58%)	32 (42%)	X ² =6.0,df=1	.014
Self report/tbx	Employment status Disability Employed Homemaker Retired Unemployed	7 (78%) /5 (56%) 23 (77%)/17(57%) 10 (100%)/9 (90%) 47 (96%)/35 (71%) 7 (100%)/4 (57%)	2 (22%)/4 (44%) 7 (23%)/13 (43%) 0 (0%) /1 (10%) 2 (4%)/14 (29%) 0 (%) /3 (43%)	Cramer's V=.32,df=4/.257,df=5	.030 /.220
Self report/tbx	Education			Cramer's	.51/.29

	Primary Secondary Third level	27 (93%)/20 (69%) 53 (89%)/41(69%) 14 (82%)/8 (48%)	2 (7%)/9 (31%) 6 (10%)/18 (31%) 3 (18%)/9 (54%)	V=.113,df=2/.186,df=3	
Self report Thromboxane	Private health insurance-yes	35(92%)	3(8%)	X ² =.10,df=1	.75
Self report Thromboxane	Alcohol intake units Mean	50 (SD63) 30 (SD27)	69 (SD80) 84 (SD86)	t=-.78,df=70 t=3.33,df=33	.44 .002
Self report Thromboxane	Weight mean (kgs)	86 (SD14) 83 (SD13)	87 (SD18) 94 (SD15)	t=-.19,df=103 t=3.98,df=104	.84 .001
Self report Thromboxane	Hyperlipidaemia	86 (90%) 62 (65%)	9 (10%) 33 (35%)	Cramer's V=.101,df=1 Cramer's V=.076,df=2	.30 .73
Self report Thromboxane	Hypertension	76 (88%) 54 (63%)	10 (12%) 32 (37%)	Cramer's V=.080,df=1 Cramer's V=,df=2	.412 .312
Self report Thromboxane	Diabetes	14 (87%) 11 (69%)	2 (12.5%) 5 (31%)	Cramer's V=.07,df=4 Cramer's V=.23,df=4	.97 .29

The results of the logistic analysis predicting objective adherence of thromboxane<2.2ng are shown in Table A7

TABLE A7 - Logistic analysis predicting objective adherence

	Exp(B)OR's	95% C.I lower	95% C.I upper	Sig p- value
PHQ-total	1.01	.78	1.31	.89
ESSI-total	.97	.90	1.04	.39
BMQ-total spec	1.02	.95	1.10	.48
BMQ-general	1.02	.94	1.10	.54
BIPQ-01	1.0	.86	1.1	.99
BIPQ-02	.97	.81	1.1	.79
BIPQ-03	1.0	.89	1.1	.62

BIPQ-04	1.0	.84	1.3	.68
BIPQ-05	1.0	.91	1.2	.40
BIPQ-06	.94	.83	1.00	.36
BIPQ-07	1.0	.92	1.20	.27
BIPQ-08	.98	.87	1.10	.79

TABLE A8 - Difference between the postal and interview group looking at adherence (objective and self reported)

DEMOGRAPHIC	POSTAL	INTERVIEW	TOTAL	statistic	p-value
% Thromboxane Effective	53/75(71%)	17/31(55%)	70/106(66%)	$X^2=.1.79, df=1$.180
% self-reported missed days	8/75(10.7%)	3/30(10.0%)	11/106(10.5%)	$X^2=.000, df=1$	1.00

There were no significant differences between the psychological mean scores of the postal group and the interview group

TABLE A9 - Multivariate analysis adjusting for living with spouse /partner, alcohol intake and weight.

	Exp(B)OR's	95% C.I lower	95% C.I upper	Sig p- value
Living with spouse/partner	.303	.065	1.42	.128
Alcohol intake in the last 4ks mean	.976	.959	.993	.005
Weight	.952	.913	.992	.019

There was no significant correlation with thromboxane and missed days when controlling for weight and age, using Logistic regression.

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
Step 1 ^a						
missedasa	-.863	.530	2.652	1	.103	.422
weightkg	-.033	.012	7.291	1	.007	.968
ageinyrsattimeofconsent	.032	.019	2.982	1	.084	1.033
Constant	1.626	1.827	.792	1	.373	5.081

a. Variable(s) entered on step 1: missedasa, weightkg, ageinyrsattimeofconsent.

Coefficients^a

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
1					
(Constant)	.368	.221		1.666	.097
gender	-.153	.075	-.149	-2.045	.042
ageinyrsattimeofconsent	.007	.003	.159	2.183	.030

a. Dependent Variable: TxB2elisaeffective

Age and gender have a significant effect on thromboxane level and aspirin effectiveness using logistic regression.

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
Step 1 ^a						
gender	-.751	.716	1.099	1	.294	.472
weightkg	-.044	.015	9.020	1	.003	.957
noofunitsconsumedin4weeks	-.008	.004	4.814	1	.028	.992
Constant	5.370	1.349	15.836	1	.000	214.876

a. Variable(s) entered on step 1: gender, weightkg, noofunitsconsumedin4weeks.

There was no significant correlation with gender using logistic regression when looking at weight and alcohol consumption.

There was no relationship between missed days and thromboxane effectiveness when controlling for age and weight with logistic regression. This is possibly due to the emerging profile of the non-adherent patient, which appears to be the younger male, who is overweight with a higher alcohol intake. It may also show us that self reported non-adherence could also be an unreliable tool due to patients responding in a sociable desirable way.