Prevalence of Aspirin Use and Its Concurrent Use with Ibuprofen among Two Middle Eastern Countries: Jordan and the UAE - A Cross Sectional Study

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ABSTRACT

The objective of this study was to assess the prevalence of aspirin use as a prophylactic agent in two countries: Jordan and the United Arab Emirates in addition to the frequency of concurrent use of aspirin and ibuprofen which might be associated with lower cardio protection. The data was collected using a structured questionnaire from December 2009 to February 2010. The results showed significantly higher proportion of Jordanian patients with cardiovascular problems (85.97%) who were using aspirin as compared to patients from the United Arab Emirates (71.26%) (p= 0.0205, chi square test). The percentage of Jordanian patients with different cardiovascular problems taking aspirin concurrently with ibuprofen was relatively high. Patients' adherence to aspirin administration in both populations was suboptimal. Patients' age and previous myocardial infarction episodes were found to have a significant (p<0.001) association with the use of aspirin in both populations.
These results call for reasonable strategies for aspirin administration in both countries.

Keywords: Pharmacodynamic Interaction, Cardiovascular Diseases, Primary Prophylaxis, Secondary Prophylaxis.

INTRODUCTION

Aspirin use is an effective and inexpensive therapy that greatly alters the course of coronary heart disease(CHD) [1;2]. Low doses of aspirin can be used in the initial treatment of cardiovascular diseases (CVD) to reduce the secondary incidence of stroke, myocardial infarction (MI), and vascular death by approximately one fourth[1].

It is evident that non-steroidal anti-inflammatory drugs (NSAIDs) interfere with the antithrombotic effects of low dose aspirin when administered concurrently[3]. It had been found that platelet aggregation was inhibited irreversibly by 98% in patients who took aspirin dose first, while it was inhibited by only 2% in those who took ibuprofen dose first. This effect was not seen upon the administration of rofecoxib and acetaminophen concluding that these drugs do not interfere with the effects of aspirin[4].

In September 2006, the Food and Drug Administration (FDA) has notified consumers and healthcare professionals (HCPs) taking ibuprofen for pain relief and aspirin as anti-platelet concurrently that ibuprofen may interfere with the anti-platelet activities of low dose aspirin taken for cardiovascular protection[5].

Patients with chronic pain e.g. rheumatoid arthritis (RA) often require NSAIDs to control their symptoms. Most of those patients are elderly with high cardiovascular risk. Thus, NSAIDs and aspirin are

frequently co-prescribed for such cases.

In addition, CVD in itself is a risk factor for upper gastrointestinal complications[6] and multiple NSAIDs therapy is also known to be a risk factor for these complications. So one might expect a higher risk of gastrointestinal events in patients taking aspirin and NSAIDs together [7]. The pattern of aspirin use for CVD protection is limitedly addressed among populations in the Middle East countries. In addition, there is no data on the rational of its use by patients in those countries.

The Arab world consists of countries at varying stages of development, and there is a great variation in the standard of population annual income, education, and health care between these countries. For this purpose, Jordon and UAE were selected as two models for those countries with total population of 5,980,000[8] in Jordan and 5.066, 000[9] in UAE.

The current study was performed to assess prevalence of aspirin use as a prophylactic treatment among Jordanian and United Arab Emirates (UAE) patients, particularly those at high risk of atherothrombotic events and have no contraindication to aspirin therapy. In addition it will, investigate the frequency of aspirin-ibuprofen concurrent use and its relation to MI episodes.

METHODS

The study was carried out in two cities of the two countries; Amman, the capital of Jordan and Dubai in the United Arab Emirates, during the period from December 2009 to February 2010. A pre-set questionnaire was developed. A pilot test for clarity of questions and reproducibility of results was performed. The questionnaire was designed in three parts: (a) patients' demographic characteristics (b) patients' medical condition including diagnosed CVD and diagnosed non-CVD (c) pattern of aspirin use: indications, number of heart attacks following aspirin prophylaxis use, adherence, concurrent use with ibuprofen or other anticoagulants .

Patients were selected randomly by simple random sampling from both governmental primary healthcare clinics and private medical centers with different specialties. 1000 and 300 patients accepted to participate

in the study from Amman and Dubai, respectively. The researchers obtained informed consent from the participants before study enrolment. The questionnaires were self-completed by the patients who agreed to take part in this study. The inclusion criteria involved Arabic patients who are residents in the country for at least the last five years and have no contraindication to aspirin therapy. In UAE, resident patients from different countries other than Arabic countries were excluded from the study.

The percent of responded patient from Amman and Dubai was 90.5 % (n=905) and 87% (n=261), respectively. All completed forms were put into sealed envelopes and returned to the primary researchers. This project had been approved by the Research Ethics Committee of Dubai Pharmacy College.

Statistical Analysis

All data was analysed using SPSS® software (version 16; SPSS, Inc, Chicago, IL). Proportional data were analysed using Pearson's Chi-Square test to compare between the groups. For all statistical analysis, p-values of 0.05 or less were considered statistically significant.

In order to determine predictors of aspirin use, a logistic regression analysis was performed. Results were considered significant at $p \leq 0.05$ and a power of 0.8.
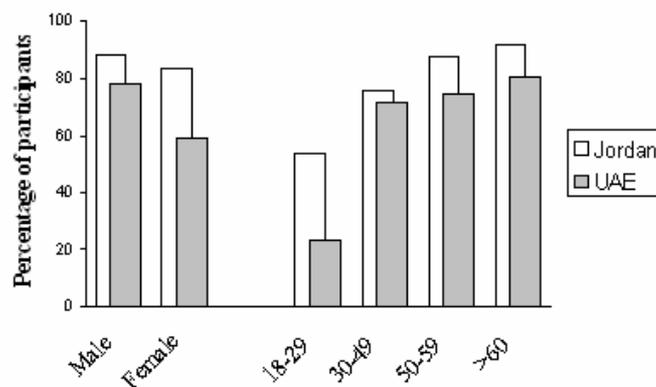
RESULTS

Patients recruited and completed the survey were 261 patients from UAE (171 males and 90 females) and 905 patients from Jordan (506 males and 399 females). These patients were of different educational levels and mostly covered by medical insurance (63.6% in UAE versus 54% in Jordan). UAE Participants were from Arabic countries with 60% are UAE nationals and 40% are UAE residents for at least the last five years and are from Arabic countries (mainly from Egypt, Sudan and Palestine). European and non-Arab patients were excluded from the study. Table 1 shows the demographic information and general characteristics of patients from both countries.

Table 1. Demographic information and general characteristics of the study participants from both countries: Jordan and UAE

	Jordan n (%)	UAE n (%)	p-value
Subject number	905	261	
Gender			
Male	506 (55.91)	171 (65.51)	
Female	399 (44.09)	90 (34.48)	
Age group			
18-29	52 (5.75)	17 (6.51)	
30-49	137 (14.14)	88 (33.72)	
50-59	266 (29.39)	105 (40.22)	
>60	450 (49.72)	51 (19.54)	
Education level			
< Highschool	272 (30.05)	112 (42.91)	
Highschool	195 (21.55)	69 (26.44)	
Graduate degree	438 (48.4)	80 (30.65)	
Medical care payment			
Cash	416 (45.97)	95 (36.4)	0.0752
Insurance	489 (54.03)	166 (63.6)	
Taking aspirin			
Yes	778 (85.97)	186 (71.26)	0.0205
No	127 (14.03)	75 (28.73)	
Proportion of heart attacks after aspirin treatment	699 (77.2)	33 (12.6)	0.0001
Concurrent use of other anticoagulant medication	204 (22.5)	69 (26.4)	0.245

There was a significant difference between the percentage of populations who were taking aspirin in Jordan and UAE (P-value=0.0205, chi square test). Also, there was a significant difference between the two populations regarding the proportion of heart attack after aspirin prophylactic treatment (p-value 0.0001, chi square test) as shown in Table 1.

Figure 1 shows that a significantly higher proportion of Jordanian males than females reported taking aspirin (89 versus 82%; p=0.034). An even larger difference was seen in UAE between males and females (79 versus 59%; p= 0.001)

Figure 1. Proportion of patients in the different gender and age groups using aspirin from both countries

Results showed significant difference (p=0.001, chi square test) in aspirin use among age groups of Jordanian patients with higher proportion in the age group range of 60 and above. Similar but more pronounced result was shown for UAE patients (p=0.001, chi square test) as shown in Figure. 1. The proportion of patients with CVD and non- CVD who used aspirin and other clinical problems is presented in Table 2.

Table 2. Proportion of patients with CVD and non-CVD who are on aspirin, aspirin plus other anticoagulants and aspirin plus ibuprofen, Jordan (n=905) and the UAE (n= 261).

Disease	n (%)		Patients on aspirin (%)		Use of other anticoagulants (%)		Use of ibuprofen (%)	
	JOR	**UAE**	**JOR**	**UAE**	**JOR**	**UAE**	**JOR**	**UAE**
CVD								
CHF	29 (3.2)	7 (2.70)	96.6	85.7	48.3	0.0	10.3	28.6
HT	281 (31.1)	100 (38.31)	88.3	72.0	12.5	13.0	44.8	18.0
CHD	89 (9.8)	30 (11.48)	94.4	73.3	37.1	36.7	27.0	6.7
TEA	39 (4.3)	3 (1.15)	92.3	66.7	28.2	33.3	43.6	0.00
VHD	20 (2.2)	1 (0.38)	100	100	35.0	100.0	30.0	0.00
Multiple CVD	235 (26)	71 (27.20)	92.3	90.1	40.9	39.4	33.6	14.1
Non-CVD								
DM	92 (10.2)	83 (31.8)	94.6	74.7	22.8	32.3	35.9	13.3
RA	26 (2.87)	24 (9.2)	65.4	58.3	23.1	7.1	76.9	50
PUD	27 (2.98)	21 (8.0)	85.2	57.1	11.1	33.3	40.7	4.76
DM and RA	359 (39.6)	11 (4.2)	89.7	81.8	28.2	33.3	38.8	27.3
Others	283 (44.41)	122 (46.7)	72.6	73	10.9	32.6	41.0	18.0

CH: Congestive Heart Failure, HT: Hypertension, CHD: Coronary Heart Diseases, TIA: Transient Ischemic Attack, VHD: Valvular Heart Disease, DM: Diabetes Mellitus, RA: Rheumatoid Arthritis and PUD: Peptic Ulcer Disease

Results revealed that the rank of most predominant clinical conditions among patients visiting clinics in both countries was as follows: hypertension > multiple CVD > non CVD. Assessing current aspirin use in respect to the disease indicated that the majority of patients with cardiovascular problems are on aspirin in both populations as shown in Table 2. For patients with non cardiovascular conditions, results showed that the majority of Jordanian patients with DM were using aspirin (94.6%). A high percentage of patients with peptic ulcer disease (PUD) reported using aspirin (85.2%) of which 40.7% are using ibuprofen concurrently with aspirin. While for UAE patients' results showed that, 74.7% of diabetics were on aspirin. A 57.1% of patients with PUD were reported using aspirin and few of them are concurrently on aspirin and ibuprofen (4.76%). The highest percentage of patient taking aspirin and ibuprofen concurrently was among those suffering from RA in both countries as shown in Table 2.

Upon questioning patients regarding their adherence to aspirin, no significant difference was found among both populations. Most of the patients from Jordan and UAE reported that they do not miss their tablets, 62.7% and 68.6% respectively (p-value > 0.05) as shown in Figure. 2.
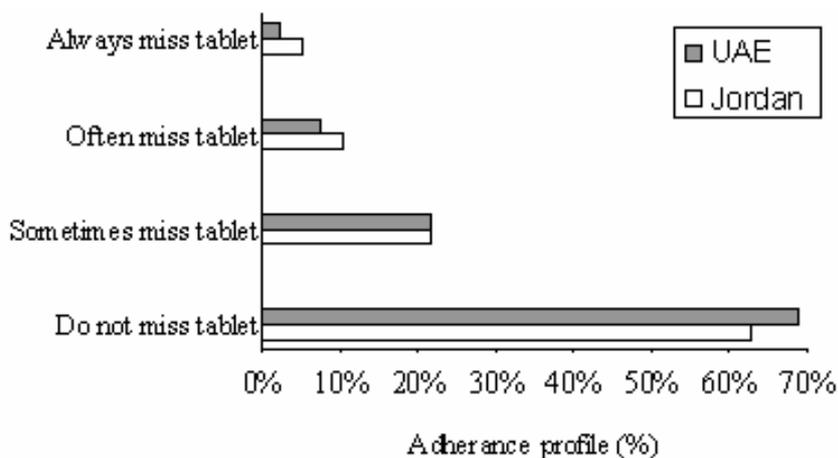
Figure 2.Adherence to aspirin among patients (proportion who do not miss, sometimes miss, often miss, and always miss their aspirin tablets)

Results showed good adherence to aspirin regimen in Jordanian population as only 15.6% of all patients reported to often/always miss their aspirin tablet. No significant difference among the different age groups (p=0.114, chi squared test) was found with regards to aspirin adherence, yet a trend was found, in that a higher proportion (31.4%) of patients aged 60 and above reported to often and always miss their aspirin tablets than younger patients do. Also, there was no significant relationship between level of education and adherence to aspirin use was seen in Jordan.

In UAE, results showed no significant difference among the different age groups (p=0.093, chi square test). 13.7% of the patients older than 60 do miss their aspirin tablets frequently. Measuring the effect of level of education on aspirin use in UAE revealed that there is no significant relationship between level of education and adherence to aspirin use was seen (p=0.146, chi square test).

There was no significant difference between the proportion of insured patients in both Jordanian and UAE regarding aspirin use. In UAE, method of payment made no difference for patients' use of aspirin as no significant difference was found in the proportion of patients taking aspirin for those who were insured and patients who were not insured (p= 0.348, chi squared test).

In Jordan, 83.2% of all patients who are taking aspirin

reported to have had a MI following to their aspirin use (Table 3). While in UAE, 17.2% of all patients using aspirin reported to have had a MI following to their use of aspirin tablets. Patients, who reported to miss taking their aspirin tablets, had a significantly higher chance of developing a MI (p= 0.006, chi squared test) (Table 3).

Table 3 Jordan and UAE results - proportion of patients who have suffered a MI followed their intake of aspirin in relation to adherence with the treatment

		Missing aspirin doses n (%)			
		No	**Sometimes**	**Often**	**Always**
Jordan					
Suffering from MI after	Yes	399 (90.7)	154 (78.2)	64 (68.8)	30 (62.5)
aspirin intake	No	41 (9.3)	43 (21.8)	29 (31.2)	18 (37.5)
Total		440	197	93	48
UAE					
Suffering from MI after	Yes	14 (12.2)	8 (17.0)	8 (44.4)	2 (33.3)
aspirin intake	No	101 (87.8)	39 (83.0)	10 (55.6)	4 (66.7)
Total		115	47	18	6

Logistic regression analysis identified "patients' age" and "previous MI episode following aspirin use" to be significantly associated with aspirin use (p<0.001), in Jordan while "patients' gender", "Age" and "previous MI episode following aspirin use" to be significantly associated with aspirin use (p<0.001) in UAE. Examining the proportion of UAE patients who use aspirin concurrently with ibuprofen to patients who use aspirin alone and have developed a MI (1.5% vs 10.7%), results showed no significant difference in the proportion of patients who reported having a MI between the two groups (p= 0.812, chi squared test).

DISCUSSION

In the present study, we aimed at assessing national trends and patterns of aspirin use as a prophylactic agent among Jordanian and UAE patients particularly who are at high risk of atherothrombotic events and have no contraindication to aspirin therapy. In addition, to assess the frequency of concurrent use of aspirin and ibuprofen which might be associated with lower cardio-protection than aspirin does alone because of a pharmacodynamic interaction.

Many studies have reported the pattern of aspirin use in different countries[10-12].In the Scandinavian Simvastatin Survival Study (4S), only 37% of patients had been receiving aspirin[12]. In the Atherosclerosis Risk in Communities (ARIC) study, aspirin use in patients with a history of myocardial infarction was 53% and in 30% of those with a history of angina[10]. In London, about half of clinic patients with coronary artery disease used aspirin.[11]

In the present study it was noted that aspirin use was not unified across patient subpopulations. As with other studies[10;13] aspirin use was less common in women than in men in both countries. This may be due to that women usually receive less aggressive treatment of CHD [14]. Only recently clinicians have had rigorous evidence to guide decision making about the use of aspirin in the primary prevention of CVD in women. It had been reported that the greatest benefit from low dose of aspirin appeared in women of 65 years old and older. In this sub-group, aspirin reduced the risk of major cardiovascular events by 26 percent [15].

A high rate of aspirin utilization in both countries by geriatric populations comes in consistence with results from other studies[13], since 84% of deaths cases were due to CHD occurred in aged people 65 and older.[16] On the other hand, aspirin should be used cautiously among individuals with a history of peptic ulcer disease, gastrointestinal bleeding, hemorrhagic stroke, or taking

NSAIDs, warfarin, and clopidogrel in which all can increase risk for bleeding. However, in the absence of significant bleeding risks, aspirin should routinely be considered for all men and women without diabetes above the ages of 48 and 57 years, respectively, for primary CVD prevention. For subjects below this age thresholds or for those above the age of 75 years, the decision to initiate aspirin treatment should be based on a patient's individual cardiovascular risk profiles[17]. Patients should be reminded to take aspirin with food to minimize the risk of gastrointestinal irritation or bleeding[18].

Hypertension and multiple cardiovascular conditions were the most predominant conditions in both Jordan and the UAE for patients visiting clinics in both countries. Assessing current aspirin use which is relevant to the disease showed that relatively high proportion of patients with cardiovascular problems are on aspirin in both populations which is a high-quality indicator of physicians' understanding of the aspirin importance in both primary as well as secondary prevention of cardiovascular diseases.

Although past studies in other countries [19] have reported comparatively higher rates of aspirin use in patients with CVD, most of these studies focused on selected patients whose use of aspirin might be higher than that in the physician clinic setting assessed here. Although the presented study has shown that there is an appropriate aspirin consumption pattern in patients with high risk factors for thrombosis, there is still a need to increase the awareness of patients and healthcare professionals regarding the inappropriateness of co-administration of ibuprofen with aspirin especially in Jordan where the present study showed that the co-administration of both drugs was relatively high. Health care professionals should advise consumers and patients regarding the in-appropriate concurrent use of ibuprofen and aspirin following FDA recommendations. Tit is recommended by FDA that 400-mg ibuprofen should be taken at least 30 minutes after or more than 8 hours before immediate-release aspirin [5].

However, the clinically meaningful and long-term effect of aspirin-ibuprofen co-administration is still unknown. Thus, the current level of evidence is not sufficient to make definitive recommendations for or against the concomitant use of ibuprofen for patients requiring prophylactic aspirin. But until a prospective, well designed controlled trial to address the clinical implications of NSAIDs–aspirin interaction performed, we should accept the findings from the epidemiologic data and change the practice, i.e., avoiding prescribing ibuprofen with aspirin and prefer diclofenac[20] or COX-2 selective inhibitors as suitable alternative for Ibuprofen[21].

Another finding is that 85.2% of Jordanian patients having PUD are using aspirin of which 40.7% are using ibuprofen concurrently. The use of aspirin in PUD patients is recommended only for those whose risk for cardiovascular events (based on coronary risk assessment tools) is sufficiently high, that it outweighs the risk for GI complications. Secondary prevention in these individuals is recommended based on a documented decrease in future cardiovascular events and mortality[22]. Patients being treated with low dose aspirin for cardio-protection should be assessed for factors that increase the risk for GI injury. Studies have confirmed that co-therapy with a proton pump inhibitor (PPI) or misoprostol decreases the risk for GI injury and complications[23].

Concurrent use of aspirin and ibuprofen will aggravate the gastrointestinal conditions and the risk for gastrointestinal bleeding. In such case, the physician can shift the patient to another antiplatlet agent or using either acetaminophen for analgesic purposes[24] or COX-2 inhibitors for an anti-inflammatory effect[4].

This was not reported in UAE where 57.1% of patients having PUD are using aspirin of which 4.76% only are using ibuprofen, which may indicate relatively higher awareness among HCPs on the disadvantage of co-administring Ibuprofen along with aspirin in UAE.

The benefits of CVD prevention depend upon high-risk patients achieving good adherence to medical regimens of proven efficacy[25]. Our study showed that long-term adherence of cardiovascular patients in both populations is suboptimal; patients who reported do not miss a dose of aspirin was 62.7% and 68.6% in Jordan and UAE, respectively.

In general, different factors influence patient adherence to treatment, including patient conviction that the medication is necessary as stressed by the advices and explanations provided by the physician and pharmacist with posterior reinforcement during follow-up[26]. In addition, it has been seen that patient age, sex, family-mediated reinforcement and lifestyle also influence adherence to therapy[26].

In our study, patient age rather than the level of education has a trend on patient adherence to their aspirin tablet in both countries. Older patients usually are intended to miss their dose more than the younger ones. To improve their adherence, patients' orientation regarding the importance of their medications should be improved by different means from which pharmacists can use a daily drug reminder chart which significantly improves medication compliance in geriatric patients[27]. The present study revealed that older patients and those with previous MI following the use of aspirin are the highest proportion of those who use aspirin in Jordan, while older male patients and those with previous MI following the use of aspirin are the highest proportion of those who use aspirin with cardiovascular problems in UAE

Evaluating the effect of patient adherence on the higher incidence of MI revealed that, in the UAE population, it was estimated that higher proportion of patients experienced MI may be in part due to missing their aspirin tablet which subject these patients to less cardiac protection and expected to have more attacks than patients who are taking aspirin regularly since strong evidence linking aspirin use with the prevention of recurrence of a cardiovascular event[28;29]. Increased adherence to cost-effective preventive measures such as aspirin therapy can contribute significantly to reducing the societal burden of CVD.

On the other hand, medical insurance status mainly impacts aspirin use in Jordan as more patients reported not taking aspirin were not insured, while in UAE, insurance made no significant impact on the level of aspirin use. This may be attributed to the economic status difference between the two populations in both countries with the UAE has higher population income.

The present study has certain limitations which are mainly represented in limited sample size from both populations. Also, there is a potential for aspirin use in both Jordanian and UAE populations to be underreported due to its availability at low costs without prescription. Although patients with reported contraindications were excluded, the investigated sample may include patients with unreported contraindications. It is very important to highlight on the fact that the present study was based on patient self-report information, and it would be appropriate if it was done based on clinical judgment by investigating patient medical records.

CONCLUSION

The current study suggests that aspirin use in patients with CVD has become a widely disseminated practice in Jordan and UAE. However, there is still an opportunity to promote the use of aspirin for the primary and secondary prevention of CVD among patients who have risk factors for CVD and no contraindications to aspirin use. Also there is a need to increase the awareness of patients and healthcare professionals regarding the effect of co-administration of ibuprofen with aspirin especially for patients with chronic use like in RA until a well-controlled trial to be performed to address the clinical importance of this interaction. Till then, prescribers should avoid prescribing ibuprofen concurrently with aspirin and recommend to prescribe diclofenac or COX-2 selective inhibitors as suitable alternative for ibuprofen.

REFERENCES

(1) Terashita K. and Imamura K. Preparation of antipyretic analgesic by direct compression and its evaluation. *Chem. Pharm. Bull. (Tokyo)*. 2005; 50(12): 1542-1549.

(2) Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002 January 12;324(7329):71-86.

(3) Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1997 October 21;96(8):2751-3.

(4) Ouellet M, Riendeau D, Percival MD. A high level of cyclooxygenase-2 inhibitor selectivity is associated with a reduced interference of platelet cyclooxygenase-1 inactivation by aspirin. *Proc Natl Acad Sci U S A* 2001 December 4;98(25):14583-8.

(5) Catella-Lawson F, Reilly MP, Kapoor SC et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001 December 20;345(25):1809-17.

(6) Food and Drug Administration U.S.Department of Health and Human Services. Concomitant use of ibuprofen and aspirin. *J Pain Palliat Care Pharmacother* 2007;21(2):73-4.

(7) Silverstein FE, Graham DY, Senior JR et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti inflammatory drugs: a randomized, double-blind, placebocontrolled trial. *Ann Intern Med* 1995;123:241-9.

(8) Davidge ST. Prostaglandin H synthase and vascular function. *Circ Res* 2001 October 12;89(8):650-60.

(9) The Hashemite Kingdom of Jordan Department of Statistics (DOS). Population Projection in 2009. *The Hashemite Kingdom of Jordan Department of Statistics (DOS)* 2010.

(10) UAE population to grow 6% in 2009. *UAE interact* 2009. AccessedJuly 13, 2010.

(11) Shahar E, Foisom AR, Romm FJ, et al. Patterns of aspirin use in middle-aged adults: The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 1996;131:915-22.

(12) McCartney P, Macdowall W, Thorogood M. A randomised controlled trial of feedback to general practitioners of their prophylactic aspirin prescribing. *BMJ* 1997 July 5;315(7099):35-6.

(13) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994 November 19;344(8934):1383-9.

(14) Cook NR, Chae C, Mueller FB. Mis-medication and under-utilization of aspirin in the prevention and treatment of cardiovascular disease. *MedGenMed* 1999. AccessedDecember 12, 8 A.D.

(15) Ayanian JZ., Epstein AM. Differences in the use of procedures between men and women hospitalized for coronary heart disease. *N Engl J Med* 1991;325:221-5.

(16) Ridker PM, Cook NR, Lee IM et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005 March 31;352(13):1293-304.

(17) National Health and Nutrition Examination Survey III (NHANES III, 1988Y94), CDC/NCHS. 2009.

(18) Bulugahapitiya U, Siyambalapitiya S, Sithole J, Fernando DJ, Idris I. Age threshold for vascular prophylaxis by aspirin in patients without diabetes. *Heart* 2008 November;94(11):1429-32.

(19) Sorensen HT, Mellemkjaer L, Blot WJ et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000 September;95(9):2218-24.

(20) Bratzler DW, de LA, Jr., Johnson MC et al. The Cooperative Cardiovascular Project in Oklahoma. *J Okla State Med Assoc* 1997 July;90(6):219-27.

(21) Schuijt MP, Huntjens-Fleuren HW, de MM, Vollaard EJ. The interaction of ibuprofen and diclofenac with aspirin in healthy volunteers. *Br J Pharmacol* 2009 July;157(6):931-4.

(22) Strand V. Are COX-2 inhibitors preferable to non-

selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin? *Lancet* 2007 December 22;370(9605):2138-51.

(23) Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002 January 12;324(7329):71-86.

(24) Graham DY, Agrawal NM, Campbell DR et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Arch Intern Med* 2002 January 28;162(2):169-75.

(25) Gaziano JM, Gibson CM. Potential for drug-drug interactions in patients taking analgesics for mild-to-moderate pain and low-dose aspirin for cardioprotection. *Am J Cardiol* 2006 May

8;97(9A):23-9.

(26) Insull W. The problem of compliance to cholesterol altering therapy. *J Intern Med* 1997 April;241(4):317-25.

(27) Kravitz RL, Hays RD, Sherbourne CD et al. Recall of recommendations and adherence to advice among patients with chronic medical conditions. *Arch Intern Med* 1993 August 23;153(16):1869-78.

(28) Gabriel M, Gagnon JP, Bryan CK. Improved patients compliance through use of a daily drug reminder chart. *Am J Public Health* 1977 October;67(10):968-9.

(29) Murray JA, Lewis C, Pearson TA, et al. Prevalence and population characteristics of aspirin use in the primary and secondary prevention of cardiovascular disease. *AmJ Epidemiol* 1995;141:71.

(30) Stafford RS. Aspirin use is low among United States outpatients with coronary artery disease. *Circulation* 2000;101:1097-101.

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