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Original article

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Prescribing Aspirin for Primary Prevention and Risk Factors of Cardiovascular Events in Diabetic Patients at Huaiyot Hospital, Trang Province

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Abstract

Background: Cardiovascular diseases (CVDs), including coronary heart disease and stroke, are a major cause of death in many countries. Currently, using aspirin, an antiplatelet, is recommended to prevent CVDs in diabetic patients but there are still no clear benefits for primary prevention. **Objectives**: To compare the incidence of cardiovascular diseases between received aspirin and non-received aspirin groups among diabetic patients without prior CVDs, to identify risk factors for CVD outcomes and to find out the adherence to the American Diabetic Association (ADA) guidelines for aspirin therapy in primary prevention among diabetic patients. **Materials and methods**: Retrospective data review was conducted by assessing electrical medical records from January 2012 to 2017. The main interesting risk factors and aspirin used and non-used data were extracted. The outcomes were the new event of CVDs. The processes of data collection and validation following the inclusion and exclusion criteria were performed by the diabetic patient care team. Data analyses were performed by t-test, chi-square test, and multiple logistic regressions. **Results**: 1,671 diabetic patients were finally enrolled in the study. There was no statistically significant difference of CVDs between aspirin and non-aspirin user with adjusted OR of 1.16 (95% CI,0.80-1.69). Albuminuria, duration of DM more than 10 years and comorbidity with hypertension and dyslipidemia increased the risk of CVDs with adjusted OR of 1.88(95%CI,1.31-2.71), 1.48(95%CI, 1.01-2.25), 3.34 (95%CI,1.75-6.38), 3.89(95%CI,2.00-7.35), respectively. Eighteen point six percent of the subjects were overused aspirin following the ADA recommendation. **Conclusions**: The use of low-dose aspirin was not associated with new CVDs events in diabetic patients without prior CVDs because no statistical significance. There is some overuse of aspirin for primary prevention. Doctors should pay attention to other comorbidities such as hypertension and dyslipidemia, especially in a patient with albuminuria and long duration of DM more than 10 years.

Keywords: Aspirin, Cardiovascular disease, Primary prevention, Diabetic patient

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Introduction

Cardiovascular diseases (CVDs) become the major cause of death, in which the World Health Organization (WHO) estimated that 17 million people died from CVDs, particularly heart attacks and strokes every year and it will increase to 25 million people per year in 2030 (WHO,2015). The number of deaths from CVDs was mainly in the developing countries because of the increasing incidence of high blood pressure, dyslipidemia, diabetes mellitus(DM), smoking, inactivity lifestyle and obesity that are considered as the major risk factors of CVDs (Lim et al, 2012). Whereby, in Thailand, as of 2012, there were 501,000 people (29%) died with CVDs of all 66,785,000 people and it was the first cause of death in both sexes and all age groups (WHO,2014).

One of the major risk factors of CVD is diabetes. The data of the American Heart Association in 2015 reported that at least 68%and 16%of more than 65 years old diabetic patients have died from coronary heart disease and stroke, respectively (Pignone et al, 2010). In diabetic patients, a chance of having CVDs was 2-4 folds more than non-diabetic ones because major CVD risk factors such as dyslipidemia, hypertension, and obesity were frequently founded in the patients (Pignone et al, 2010). In addition, diabetes is associated with an increased platelet activity, inflammatory and pro-thrombotic environment, exacerbating the development of atherothrombosis (Pignone et al, 2010; Guirguis-Blake et al, 2015). Therefore, antiplatelet treatment strategies were developed and used in many diabetic patient treatment guidelines, especially low dose aspirin that has been playing a role to prevent CVDs in DM patients for many years (Pignone et al, 2010; Guirguis-Blake et al, 2015). Currently, the American Diabetic Association (ADA) has recommended indication of low dose aspirin (75–162 mg/day) to prevent CVDs by considered from Atherosclerotic Cardiovascular Disease risk (ASCVD risk) that is calculated from age, sex, co-morbidities, smoking, blood pressure and level of cholesterol that predicted chance to occur CVDs in 10 years (American Diabetes Association, 2014). Meanwhile, in 2013, the European Society of Cardiology suggested that low dose aspirin should be considered only in high CVD risk patients and it has benefited more than the risk of bleeding complication (Fifth Joint Task Force of the European Society, 2012).

From the previous fourteen studies, using aspirin for primary prevention was associated with reducing 10% of CVD events but increased 6% of hemorrhagic stroke and there are now no clear pieces of evidence on the benefits of low dose aspirin for primary prevention in DM patients and the adverse events with continuous aspirin use (Ogawa et al, 2008; Xie et al, 2014). In the past five years, 43% of DM patients have prescribed aspirin for primary prevention in Huaiyot Hospital and there was no data about the incidence of CVDs in both groups (aspirin and non-aspirin). As a result, this study aimed to compare the incidence of CVDs between received aspirin and non-received aspirin groups of DM patients without prior CVDs, to identify risk factors for CVD outcomes and to find out the adherence to the ADA guidelines for aspirin therapy in primary prevention among diabetic patients.

Methods.

The study was conducted in January 2017. The secondary data from the database of the HOSxP program of Huaiyot Hospital, Trang Province, South of Thailand, were used through reviewing electrical medical records (EMRs). The hospital numbers (patient's identifications) of all patients diagnosed with DM before January 2012 following the ICD 10 codes (E10-E14) and have had no prior CVDs (cerebrovascular disease and ischemic heart disease I20-I25, I60-I69) were extracted. The data were then entered into the designed recording forms. The processes of data collection and validation were performed by diabetic patient care team consisted of doctor, nurses, pharmacist, and information technology (IT) staff.

The diabetic patients were excluded from the study if, i) age less than 18 years, ii) false diagnosis to DM, iii) died before the date

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of study, iv) lost follow up and uncompleted data after the date of study and v) received anticoagulant drugs.

In the study, aspirin users defined as patients who received aspirin less than 162 mg per day before the date of study (January 2012) until January 2017.The needed aspirin patients defined as patients who were recommended for aspirin use following the ADA guideline 2014. The main interested risk factors were age, sex, duration of disease, aspirin received data, body mass index (BMI), blood pressure, dyslipidemia (total cholesterol > 200 mg/dl, LDL > 100 mg/dl,TG > 150 mg/dl, HDL < 40 mg/dl), smoking, albuminuria (albumin creatinine ratio from spot urine > 30 µg/mg creatinine) , blood glucose, HbA1C, cholesterol, and ASCVD risk score calculated from the start date of data collection, January 2012.

The outcomes of the study were new CVD cases onset after the date of study (January 2012) and non- CVD cases. A CVD group was patients who were diagnosed with CVDs following ICD-10 codes of stroke and ischemic heart disease from January 2012 to January 2017. Any patient who died from all causes after the date of the study was also included into the study.

Statistical analysis

All analyses were undertaken by R-program version 3.3.3. In data analysis processes, continuous data were firstly tested for normal distribution by Shapiro test. Univariate analyses were performed to compare means of the baseline characteristics by t-test and presented the results as mean (standard deviation, SD). For categorical baseline characteristics, chi-square tests were performed. To identify interested risk factors for CVD outcomes among diabetic patients, multiple logistic regressions were finally performed and the results were displayed as odds ratio (OR) with 95% confidence interval (CI). The adjusted odd ratios were done by adjusted with the main interested risk factor of CVDs, and the appropriately fitted model as finally selected for presenting as the results.

Results

A total of 1,671 patients were enrolled to the study after excluded those who had uncompleted data (159 patients), a false diagnosis of DM (66 patients), died before the date of study (35 patients) and patients received other anticoagulants (warfarin) (5 patients) (Figure 1). For baseline characteristics of the study subjects, CVD patients were more likely to be men, smokers, aspirin users, presented with albuminuria, hypertension, and dyslipidemia (Table1). Mean age was higher in CVD group. The longer duration of DM was observed in CVD group. There were no significant differences of both groups in means of BMI, SBP, blood glucose, HbA1C, cholesterol, HDL and LDL levels, but there was a higher triglyceride level in CVD group(Table2). There were 35.6% in needed aspirin group that have received aspirin properly. Eighteen point six percent of the diabetic patients were prescribed aspirin in unneeded aspirin group or overuse (Chart1).

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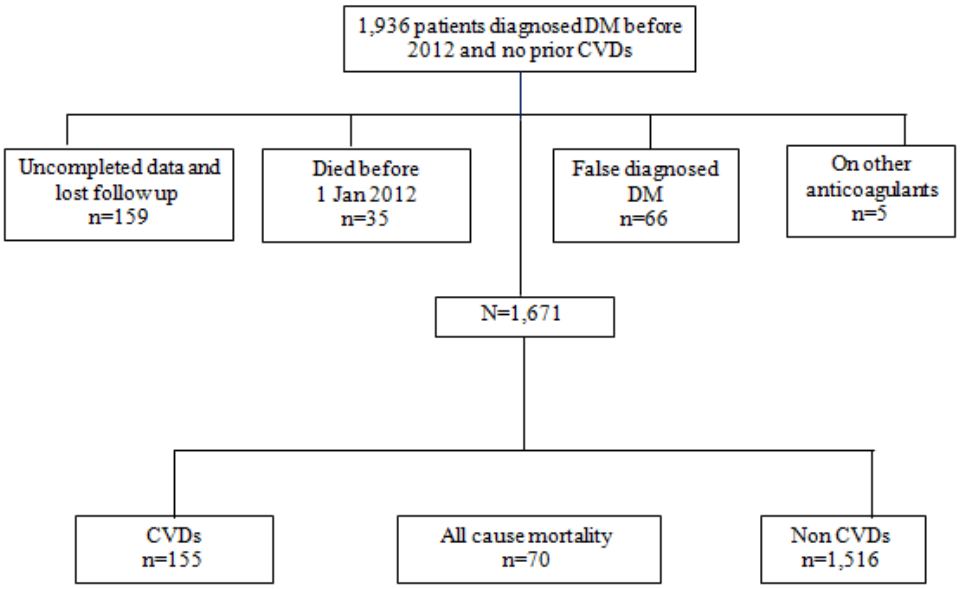

Figure 1. Flow chart of extracting the study subjects

Table 1. Baseline characteristics of the study subjects

Characteristic	All patients n =1,671 (%)	Non CVDs n = 1,516 (%)	CVDs n =155 (%)	*p-value*
Sex				0.001
Female	1108(66.3)	1024(67.5)	84(54.2)	
Male	563(33.7)	492 (32.5)	71(45.8)	
Aspirin user				0.050
Non Aspirin	803(48.1)	740(48.8)	63(40.6)	
Aspirin	868(51.9)	776(51.2)	92(59.4)	
Smoke				0.010
Non smoke	1,465(87.7)	1,339(88.3)	126(81.3)	
Smoke	206(12.3)	1,77(11.7)	29(18.7)	
Hypertension				< 0.001
Non hypertension	404(24.2)	390(25.7)	14(9.0)	
Hypertension	1,267(75.8)	1,126(74.3)	141(91.0)	
ASCVD score				< 0.001
<10%	859(51.4)	807(53.2)	52(33.5)	
10-<20%	550(32.9)	485(32.0)	65(41.9)	
20-<30%	171(10.2)	146(9.6)	25(16.1)	
30-<40%	79(4.7)	68(4.5)	11(7.1)	
>40%	12(0.7)	10(0.7)	2(1.3)	

ASCVD = Atherosclerotic cardiovascular disease
BMI = Body mass index
*NA = Not available

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Table 1. Baseline characteristics of the study subjects (cont.)

Characteristic	All patients n =1,671 (%)	Non CVDs n = 1,516 (%)	CVDs n =155 (%)	*p-value*
Dyslipidemia				
No	444(26.6)	431(28.4)	13(8.4)	< 0.001
Dyslipidemia	1,227(73.4)	1,085(71.6)	142(91.6)	
Albuminuria				
No	994(59.5)	928(61.2)	66(42.6)	< 0.001
Albuminuria	659(39.4)	570(37.6)	89(57.4)	
NA*	18(1.1)	18(100)	0(0)	
BMI level				0.350
Underweight	59(3.6)	56(3.7)	3(1.9)	
Normal	376(22.6)	336(22.3)	40(10.6)	
Overweight	316(19.0)	292(19.4)	24(15.5)	
Obesity	911(54.8)	823(54.6)	88(56.8)	

ASCVD = Atherosclerotic cardiovascular disease
BMI = Body mass index
*NA = Not available

Table 2. Means and standard deviations of baseline characteristics of the study subjects

Characteristic	All patients mean (SD)	Non CVDs mean (SD)	CVDs mean (SD)	*p-value*
Age(years)	59.3(13.3)	58.9(13.4)	63.0(11.8)	< 0.01
BMI(kg/m^2)	25.9(4.7)	25.9(4.7)	25.9(4.5)	0.89
SBP(mmHg)	137(21)	137(20)	140(20)	0.05
Duration of disease (	6.4(4.8)	6.3 (4.7)	7.2(5.1)	0.02
FBS(mg/dl)	172.0(69)	172.5 (70.2)	164.6(59.2)	0.18
HbA1C(%)	8.4(2.3)	8.5(2.3)	8.3(2.2)	0.53
Cholesterol(mg/dl)	194.6(44.8)	194.3(44.2)	197.4(44.8)	0.41
LDL(mg/dl)	105.6(38.8)	105.5(38.6)	106.6(40.3)	0.73
TG(mg/dl)	183.9(102.8)	182.1(103.4)	200.9(95.2)	0.03
HDL(mg/dl)	52.0(14.2)	52.1(14.1)	49.9(14.39)	0.07

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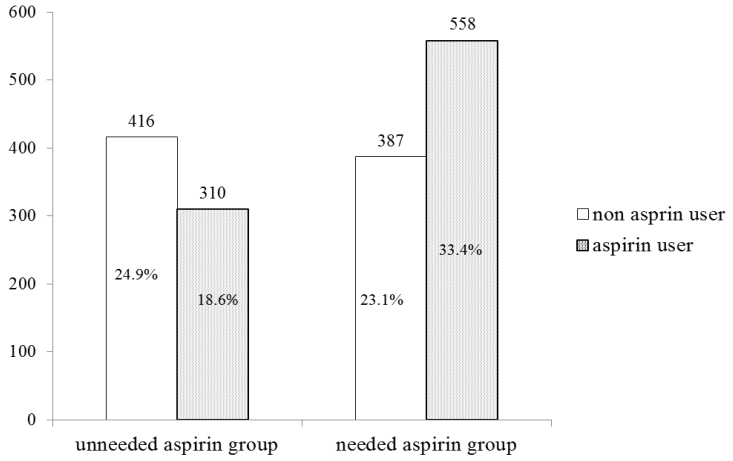

Chart 1 Prescribing aspirin adhered to the ADA recommendation for primary prevention in DM patients

Comparison of individuals who have not been used and used aspirin, aspirin users were more likely to have CVDs (cOR=1.48, 95% CI,1.04-2.11); however, after adjusted by age, sex, hypertension, smoking, BMI, ASCVD score, there was no statistically significant difference. Having hypertension, dyslipidemia, albuminuria, long duration of DM (> 10 years) were significantly increased the risk of CVDs with adjusted OR of 3.34(95%CI,1.75-6.38), 3.89(95%CI, 2.00-7.35), 1.88(95%CI, 1.31-2.71) and 1.48(95%CI, 1.01-2.25), respectively. Other risk factors liked age more than 60 years, male sex, smoking, high HbA1C seemed to be somewhat higher risk of CVDs, but not statistical significance (Table 3).

Table 3. Risk factors for CVDs among diabetic patients

Risk factor	Total CVDs (n =155)n(%)	Crude OR(95%CI)	Adjusted OR (95%CI)
Aspirin user	92(10.6)	1.48 (1.04, 2.11)	1.16 (0.80, 1.69)
Male	71(45.8)	1.62 (1.14, 2.30)	1.45 (0.96, 2.18)
ASCVD risk			
< 10%	52(33.5)	1	1
10-20%	65(41.9)	2.12 (1.42, 3.14)	1.65 (0.94, 2.89)
20-30%	25(16.1)	2.59 (1.53, 4.4)	1.60 (0.71, 3.62)
30-40%	11(7.1)	2.02 (0.92, 4.47)	1.04 (0.36, 3.01)
> 40%	2(1.3)	3.43 (0.72, 16.32)	1.60 (0.27, 9.50)
Age> 60 years	88(11.9)	1.72 (1.21, 2.44)	1.13 (0.64,1.99)
Smoking	29(14.1)	1.59 (0.99, 2.54)	1.40 (0.82, 2.40)
HbA1C > 7%	99(9.4)	1.03 (0.71, 1.49)	1.19 (0.81, 1.74)
SBP >140 mmHg	76(11.5)	1.49 (1.06, 2.11)	1.13 (0.74, 1.71)
LDL >100 mg/dl	76(9.2)	0.96 (0.68, 1.36)	1.04 (0.73, 1.49)
Hypertension	141(9.3)	3.83 (2.05, 7.17)	3.34 (1.75, 6.38)
Dyslipidemia	1,227(73.4)	4.44(2.37, 8.33)	3.89(2.00, 7.35)
Albuminuria	659(39.4)	2.17(1.53, 3.07)	1.88(1.31, 2.71)
Duration of disease	1,371(82.1)	1.81(1.22, 2.68)	1.48(1.01, 2.25)
> 10 years			

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Discussion

The present study showed that an incidence of CVDs between aspirin and non-aspirin users was not significantly associated with the CVDs outcome among diabetic patients. Even though this result was different from some other previous studies that have reduced the incidence of CVDs in the aspirin user group,15.4 % versus (VS) 13.8% for all CVD event rates, RR = 0.9 (95%CI, 0.20-0.89) from the TPT study (Pignone et la, 2010). A study in Japan in 2008, all CVD events in aspirin and non-aspirin group was 5.4% and 6.7% with HR of 0.80 (95%CI, 0.58-1.10) (Ogawa et al, 2008). However, the above two mentioned studies, there were only small differences between both groups and no statistically significant benefits. The reasons that might explain the difference of this result from the previous studies that, in fact, there were many factors not only aspirin user but also other risk factors played a role for the CVD outcomes, in which in the study after adjusted with the other factors, the estimated risk was decreased (adjusted OR = 1.16, 95%CI, 0.80-1.69).

For the other risk factors that affected CVD outcomes, the authors found that hypertension was significantly increased risk of CVDs that was similar to the previous studies, a study among Chinese population showed significantly higher average or mean SBP in coronary heart disease, stroke VS non-CVDs as 130 mmHg (95% CI 127.1–134.4), 140.6 (95% CI 137.1–144.1) VS 121.6 (95% CI 121.3–122.0) (p<0.001) (Yang et al, 2012).

Dyslipidemia as a comorbidity of DM was one of the most significant risks of CVDs (OR=3.89, (95%CI2.0-7.35), even the mean LDL level was a bit over the therapeutic goal (103 mg/dl) but not different between CVD and non-CVD groups. The previous study showed that the diabetic patients over 40 years with estimated 10 years' risk, over 7.5 % should be treated with high intensity of statin and less than 7.5% with a moderate statin (Stone et al, 2008). The clinicians, therefore, should consider more on medication to treat with the proper intensity of statin rather than LDL level only.

Moreover, the authors found some risk factors such as albuminuria, long duration of DM (> 10 years) were statistically significant differences between CVD and non-CVD groups. Albuminuria is a microvascular complication of DM and there is a strong association of proteinuria and cardiovascular morbidity and mortality in both type-2 DM patients with and without nephropathy. Also, there was supported data from the Multinational Study of Vascular Disease in Diabetics for evidence of proteinuria and ischemic heart disease in type 2 diabetes (Morrish et al, 1991).

In the study, aspirin was prescribed for primary prevention about 51.9% in the diabetic clinic. There were 18.6 % received aspirin without indication following the recommendation of the ADA guidelines 2014 or overuse. All of the overused cases were among young patients in both sexes (male □ 50 years, female ≤ 60 years) and low ASCVD risk score that has had no benefit and might be increased risk of bleeding complication. The study in the United States from 2010 to 2012 was also evidenced aspirin overutilization without CVDs that older age, more frequently visiting providers and obesity, were the significant factors for inappropriate aspirin use (Van et al, 2014).

There were some limitations of the study that could affect the results, such as unknown compliance of aspirin users and statins using. We used secondary data from the local hospital database, so it could miss the diagnosis of CVDs from ICD-10 codes owing to the doctors were not recorded the diagnosis in the database; however, the team has reviewed EMRs manually by the clinical team for reducing under diagnosis.

Conclusions

The use of low-dose aspirin was not significantly associated with CVD events in diabetic patients without prior CVDs. Overall there is some overuse of aspirin for primary prevention. Consequently, the doctor should re-evaluate on prescribing aspirin only in high-risk patients because the study shows no benefit for primary prevention. Further study about the adverse effect of aspirin should be conducted.

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Even aspirin has not decreased the risk of CVDs, but doctors should pay attention to other comorbidities such as hypertension and dyslipidemia, especially in a patient with albuminuria and long duration of DM more than 10 years.

What is already known on this topic?

There is no clear benefit of aspirin for primary prevention of CVDs in DM patients.

What this study adds?

The present study indicated that there is some overuse of aspirin for primary prevention in clinical practice. Using low-dose aspirin was not associated with CVD outcome. Hypertension, dyslipidemia, albuminuria and long duration of DM more than 10 years increased the risk of CVDs more than using or non-using aspirin.

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Potential conflicts of interest

The authors declare no conflict of interest.

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