

## ORIGINAL RESEARCH

# Aspirin Use Rates in Diabetes: A Systematic Review and Cross-Sectional Study

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## ABSTRACT

**OBJECTIVE:** Recent studies have shown that low-dose aspirin is not effective for the primary prevention of cardiovascular (CV) events in diabetes. Pharmacologic evidence suggests, however, that an adequate antiplatelet effect in diabetes requires a dose of >100 mg daily. This study was designed to identify the dose of aspirin most commonly used in diabetes.

**METHODS:** This study included a systematic review of the literature and a cross-sectional study in community pharmacies across Alberta, Canada. Medline and Web of Science were used to identify studies reporting aspirin use rates in diabetes. The average rate across studies was calculated by weighting study-specific rates by number of participants in each study. Additional information was gathered from a survey completed by senior-year pharmacy students using information on cardiovascular disease (CVD) and aspirin use collected from people with diabetes.

**RESULTS:** The systematic review identified 33 studies reporting a weighted average aspirin use rate of 41%. Among those with an indication for primary or secondary prevention, aspirin was used by 27 and 73%, respectively. The mean age of the 182 survey participants was 61±14 years; 50% were women, 81% had type 2 diabetes and 19% had had a previous CV event. Of the 176 participants with ≥1 indication for aspirin use, 118 (67%) were using aspirin regularly. The most common dose, taken by 106 of the 118 regular aspirin users (90%), was 81 mg daily.

**CONCLUSIONS:** Aspirin use is more common in people with an indication for secondary prevention. However, the most common dose used is <100 mg daily, which may not provide adequate CV protection.

**KEY WORDS:** Aspirin, cardiovascular risk, diabetes

## RÉSUMÉ

**OBJECTIF :** De récentes études ont démontré qu'Aspirin à faible dose n'est pas efficace pour la prévention primaire des accidents cardiovasculaires chez les personnes atteintes de

diabète. Cependant, selon les données pharmacologiques, pour inhiber l'agrégation plaquettaire en présence de diabète, la dose quotidienne doit être supérieure à 100 mg. Cette étude avait pour objet de déterminer la dose d'Aspirin la plus souvent administrée aux personnes diabétiques.

**MÉTHODES :** Cette étude comportait un examen systématique de la littérature et une enquête transversale menée dans des pharmacies communautaires de l'Alberta, au Canada. L'examen systématique, qui a porté sur les bases de données Medline et Web of Science, a permis de repérer les études faisant mention de la fréquence de la prise d'Aspirin chez les personnes diabétiques. La fréquence moyenne pour toutes les études a été calculée en pondérant la fréquence particulière à chacune des études en fonction du nombre de sujets de chacune. D'autres données ont été tirées d'un questionnaire rempli par des étudiants en dernière année de pharmacie sur les renseignements qu'ils avaient recueillis auprès de personnes diabétiques sur la maladie cardiovasculaire et la prise d'Aspirin.

**RÉSULTATS :** L'examen systématique a permis de repérer 33 études; pour ces études, la fréquence pondérée de la prise d'Aspirin était de 41 %. Dans 27 % des cas, Aspirin était administré pour la prévention primaire et dans 73 % des cas, pour la prévention secondaire. L'âge moyen des 182 personnes ayant participé à l'enquête était de 61 (± 14) ans; 50 % étaient des femmes, 81 % souffraient de diabète de type 2 et 19 % avaient déjà présenté un accident cardiovasculaire. Parmi les 176 participants chez qui il y avait au moins une indication pour la prise d'Aspirin, 118 (67 %) prenaient régulièrement Aspirin. La dose quotidienne la plus courante, prise par 106 des 118 personnes (90 %) qui prenaient régulièrement Aspirin, était de 81 mg.

**CONCLUSIONS :** Aspirin est plus souvent pris pour la prévention secondaire. Toutefois, la dose quotidienne la plus courante est inférieure à 100 mg et pourrait ne pas procurer une bonne protection cardiovasculaire.

**MOTS CLÉS :** Aspirin, risque cardiovasculaire, diabète

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## INTRODUCTION

Aspirin therapy is recommended for the primary and secondary prevention of cardiovascular (CV) events in most people with diabetes (1-3). Consensus guideline recommendations are based on numerous clinical trials and meta-analyses demonstrating that antiplatelet therapy significantly reduced the risk of CV events without an excessive risk of adverse events. However, results from recent clinical trials focused on efficacy in diabetes suggest that low-dose aspirin ( $\leq 100$  mg daily) is not effective for primary prevention (4,5). Moreover, use of low-dose aspirin for primary prevention may impart more harm than benefit (6). In consideration of this new information, the role of aspirin for preventing CV events in diabetes is being questioned (7).

One possible explanation for the lack of benefit seen with daily aspirin doses  $\leq 100$  mg is aspirin resistance. It appears that people with diabetes have elevated platelet reactivity and therefore lower response to aspirin compared to the general population (8). Although the exact mechanism is unknown, a subgroup analysis of the Aspirin-Induced Platelet Effect (ASPECT) study demonstrated that subjects with diabetes exhibited a significantly higher rate of aspirin resistance when given 81 mg daily compared to  $>100$  mg daily (9).

The possibility of an aspirin dose–antiplatelet response relationship has important implications for CV risk reduction strategies in diabetes. People using aspirin doses  $\leq 100$  mg daily may receive no benefit, yet still be at risk for adverse effects. To help understand the potential magnitude of this problem, it is important to determine how people with diabetes are using aspirin for the prevention of CV events. Therefore, the purpose of this study was 2-fold: first, to determine the prevalence of aspirin use for preventing CV events in diabetes; and second, to identify the dose most commonly taken.

## METHODS

Our original intent was to use a systematic literature review to answer the 2 research questions. However, the initial systematic review, conducted in May 2008, identified only 1 study reporting the daily dose of aspirin used for the prevention of CV events (10). Although this study reported a mean daily dose (169 mg; range 75 to 650 mg), it did not provide sufficient information to determine whether the common dose used was above or below 100 mg daily. Therefore, we chose to supplement our literature review with a small cross-sectional survey using available resources. Below we report the methods and results for both the systematic review and the cross-sectional survey.

### Systematic review

Two search strategies were conducted on Medline to identify articles describing aspirin use in people with diabetes

(Table 1). The first strategy combined terms for aspirin use and diabetes in the title to identify articles specifically focused on our topic of interest. The second strategy used a broader search perspective by combining terms for aspirin, diabetes and CV risk. Both search strategies were combined, and the titles and abstracts were screened to identify potentially relevant articles published in English. We supplemented the Medline search by examining the reference list of all potentially relevant articles and using Web of Science–Cited Reference Search to find articles citing the potentially relevant articles. Once the search was completed, the full article for all relevant citations was reviewed to determine if it reported the proportion of subjects with diabetes using aspirin for prevention of CV events.

One investigator used a standardized form to collect information on number of subjects with diabetes, proportion of subjects using aspirin for prevention of CV events, dose of aspirin used and type of prevention (primary or secondary prevention). The second investigator verified accuracy. The average prevalence of aspirin use across studies was calculated by weighting the study-specific prevalence by the number of subjects in the study.

### Cross-sectional survey of aspirin use

Senior-year pharmacy students at the University of Alberta are required to complete 16 weeks of experiential learning in various practice settings, including community pharmacies located in a variety of urban and rural settings across the

**Table 1. Medline search strategy (updated April 19, 2010)**

Search	Terms	Results
1	Diabetes.mp. or exp diabetes mellitus/	318 475
2	Diabetic.mp.	145 626
3	1 or 2	334 784
4	((“use” or usage or underuse or utilization) adj3 (aspirin or acetylsalicylic)).ti.	367
5	3 and 4	43
6	exp aspirin/ or aspirin.mp.	44 000
7	Antiplatelet.mp.	10 187
8	6 or 7	50 613
9	exp risk factors/ or cardiovascular risk.mp.	421 312
10	and/3,8–9	1025
11	5 or 10	1052
12	Limit 11 to English language	874
13	Limit 12 to “review articles”	281
14	12 not 13	593

province. As part of their community pharmacy rotation, students were instructed to work with at least 3 people with diabetes. We used this opportunity to supplement information on aspirin use garnered from the systematic review. Apart from obtaining patient consent, all survey-related activities were congruent with the student's regular patient care activities. This pragmatic study design was intended to foster both student and preceptor involvement (11). Prior to beginning their rotations in September 2008, all students attended an orientation seminar in which they reviewed the critical elements of informed consent and were given an overview of the survey purpose and methods. The University of Alberta Health Research Ethics Board approved the conduct of this study, and all participants provided written consent.

The survey contained 3 sections and was designed to be completed by the students using information collected during their regular patient interviews. The first section was used to record the year of birth, sex and diabetes type (type 1 or type 2) of the study participant. For the second section, we followed the 2003 Canadian Diabetes Association (CDA) clinical practice guideline recommendations (1) to identify relevant indications for aspirin use: history of a heart attack, stroke, hypertension (or use of antihypertensive medications) or dyslipidemia (or use of cholesterol-lowering medications), and current smoking status. The third section recorded aspirin use by asking "Is aspirin taken on a regular basis (more than 3 times per week)?" For those participants reporting regular use of aspirin, students were instructed to specify the daily dose taken. This section was also used to record the use of other antiplatelet agents (e.g. clopidogrel) or warfarin. After obtaining patient consent, students transferred information from their patient profile to the survey form and transmitted this information to the University of Alberta via secure fax. All data were analyzed using an Excel spreadsheet to calculate summary statistics.

## RESULTS

### Systematic review

Our literature search was updated in April 2010 and identified 620 unique citations. From these, 52 articles were considered relevant, but only 33 reported aspirin use rates for prevention of CV events in 113 939 people with diabetes (10,12-43). On average, 41% of people with diabetes used aspirin for prevention of CV events (Figure 1). In the 17 studies (n=29 966) reporting prevalence of aspirin use for primary prevention, the average rate was 27% (Figure 2) (10,12,14,17,20,21,23,26,27,29,30,33,34,37,41). The average rate was 73% in the 19 studies (n=15 427) reporting prevalence of aspirin use for secondary prevention (Figure 3) (10,12,14-17,20-23,25,27-30, 33,34,37,41).

The updated search strategy identified 5 studies reporting the daily dose of aspirin taken for prevention of CV

events, including the Australian study mentioned previously (Table 2) (10,14,20,35,42). Two studies reported only the mean dose of aspirin taken (10,14). In the remaining 3 studies, 63% of subjects were taking  $\leq 100$  mg daily for the prevention of CV events (20,35,42).

### Cross-sectional survey of aspirin use

A total of 182 Albertans with diabetes participated in the cross-sectional survey. Mean age was  $61 \pm 14$  years, 91 (50%) were women, 148 (81%) had type 2 diabetes, 23 (13%) had a previous myocardial infarction, and 17 (9%) had a previous stroke or transient ischemic attack. According to the 2003 CDA guideline recommendations (1), 176 (97%) participants had  $\geq 1$  indications for aspirin use: age  $>45$  years (159 [87%]); current smoker (29 [16%]); hypertension (129 [71%]); dyslipidemia (133 [73%]); or history of cardiovascular disease (CVD) (35 [19%]). Of the 141 subjects with an indication for primary prevention, 17 (12%) had 1 indication (age, current smoker, hypertension or dyslipidemia), 51 (36%) had 2 indications and 73 (52%) had 3 or more.

Aspirin was used regularly by 118 (67%) of the 176 participants with  $\geq 1$  indications for aspirin use. Of the 35 participants with a history of CVD, 27 (77%) were using aspirin for secondary prevention, 8 (23%) were using clopidogrel either alone (n=4) or in combination with aspirin (n=4), and 4 (11%) participants were not using any antiplatelet agent. Of the 141 participants who had an indication for aspirin in primary prevention, 91 (65%) reported using aspirin regularly, and none were using clopidogrel. The most common dose, taken by 106 of the 118 (90%) participants regularly using aspirin, was 81 mg daily (Table 2). Nine (8%) participants took 325 mg of aspirin daily, and 3 were unsure of their daily dose.

## DISCUSSION

Using the combination of a systematic review and small cross-sectional study, we characterized aspirin use for prevention of CV events in diabetes. Summarizing the information from 33 studies (n=113 939), we determined that 27% of subjects with diabetes who had an indication for primary prevention and 73% of those who had an indication for secondary prevention were taking aspirin regularly. Through our review of the literature and data collected in the cross-sectional survey, we found that the majority (over 60%) of people regularly using aspirin for the prevention of CV events take  $\leq 100$  mg daily.

The potential dose-response relationship for antiplatelet activity seen in the ASPECT study has important implications for the management of type 2 diabetes (9). For example, it may explain, in part, the neutral results of studies examining the effect of  $\leq 100$  mg aspirin daily for primary prevention of CV events in people with diabetes (4,5,44). However, the

Figure 1. Reported aspirin use rates all subjects

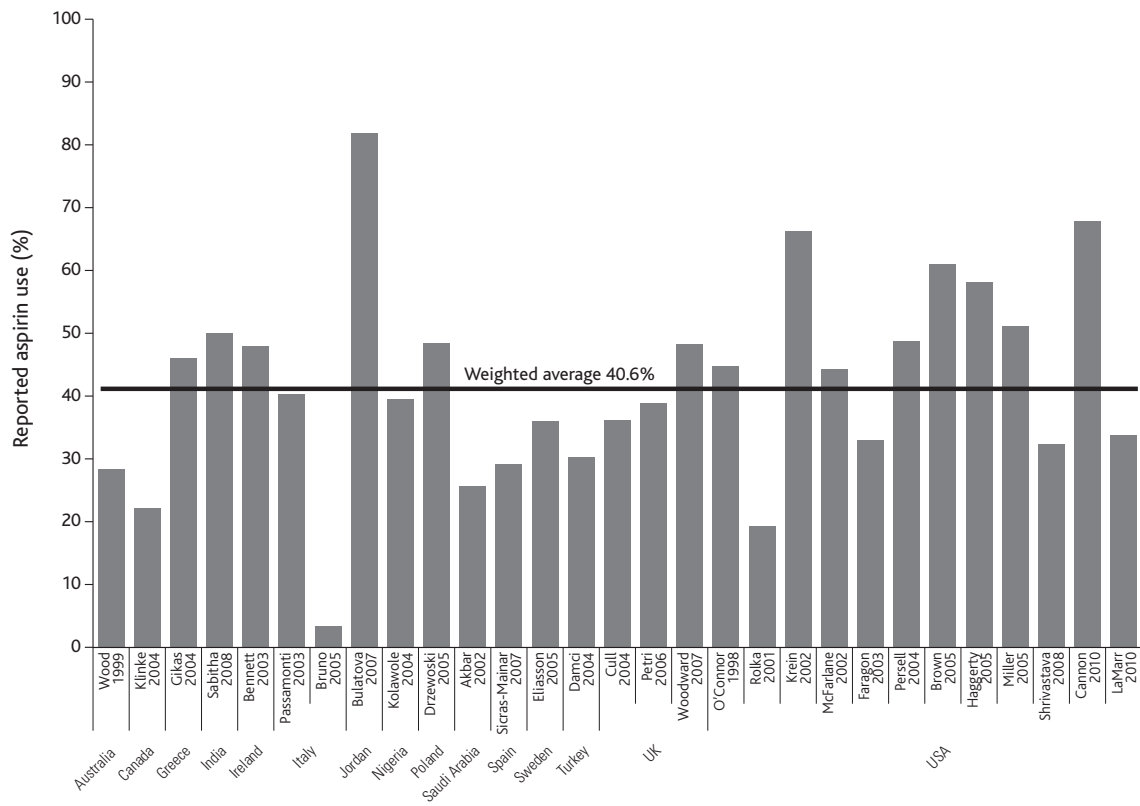


Figure 2. Reported aspirin use rates for primary prevention

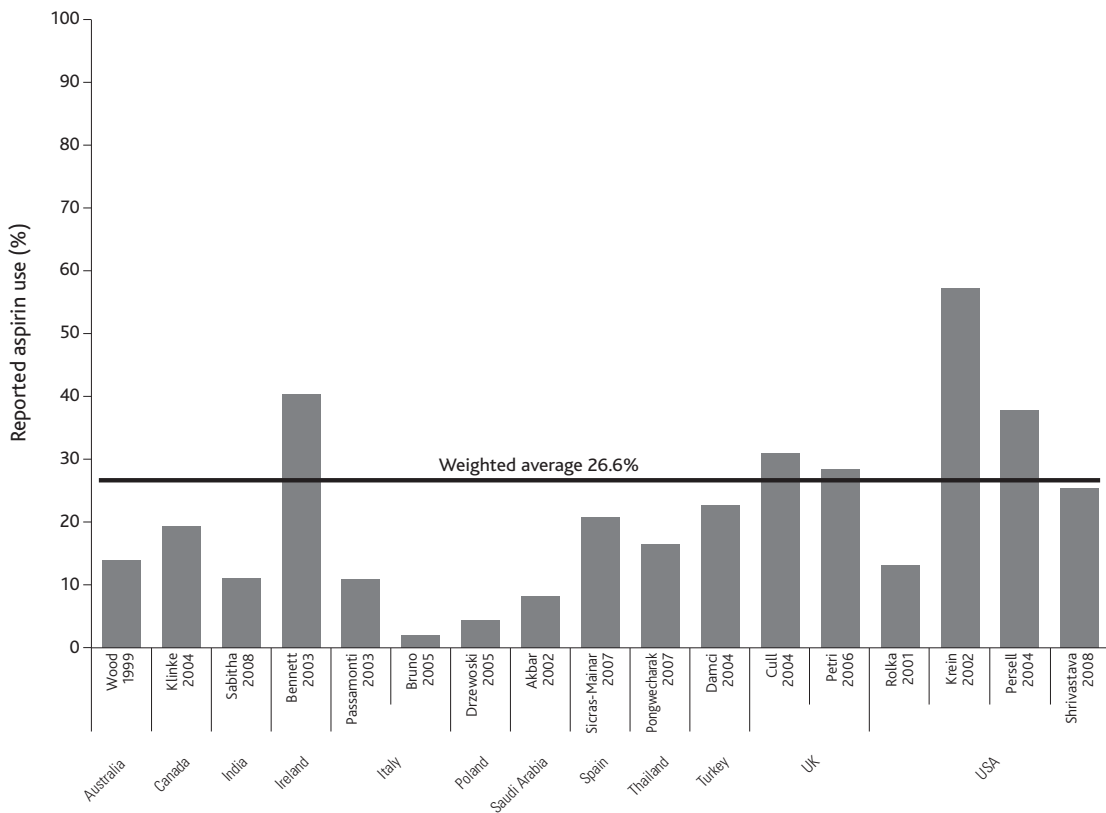


Figure 3. Reported aspirin use rates for secondary prevention

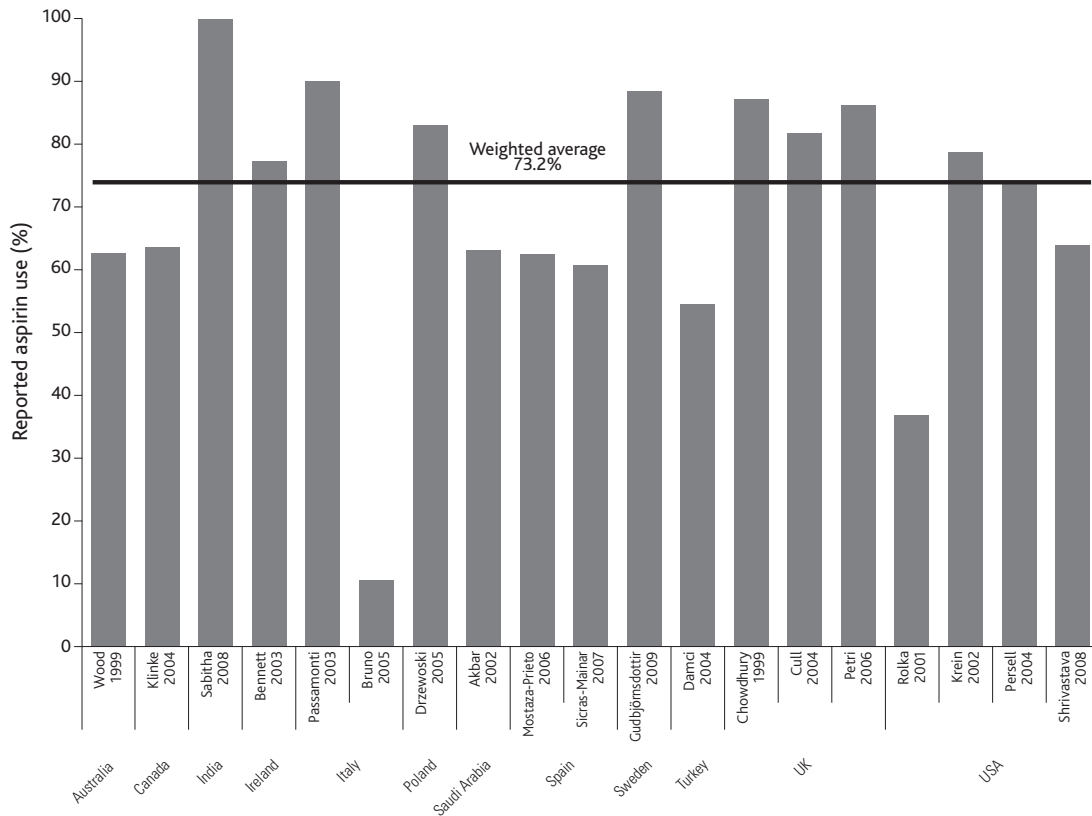


Table 2. Aspirin dose used for prevention of cardiovascular events

Author (year)	Location	Daily aspirin dose used, n (%) <sup>*†</sup>				
Wood (1999)	Australia	Mean dose 169 mg (range 75–650 mg)				
McFarlane (2002)	USA	81 mg daily: 128 (21.1) 325 mg daily: 480 (78.9)				
Drzewoski (2005)	Poland	Mean dose 126.7 mg (range 75–500 mg) 75 mg daily: 192 (61.5) 100 mg daily: 72 (23.1) >100 mg daily: 48 (15.4)				
Sabitha (2008)	India	75–150 mg daily: 50 (100)				
Cannon (2010)	USA	1–74 mg daily: 46 (0.6) 75–100 mg daily: 5236 (64.6) 101–324 mg daily: 152 (1.9) ≥325 mg daily: 2668 (32.9)				
Current study (2008–2009)	Canada	<table border="1"> <tr> <td>Primary prevention (n=91)</td> <td>81 mg daily: 82 (90) 325 mg daily: 7 (8) Unsure of dose: 2 (2)</td> </tr> <tr> <td>Secondary prevention (n=27)</td> <td>81 mg daily: 24 (89) 325 mg daily: 2 (7) Unsure of dose: 1 (4)</td> </tr> </table>	Primary prevention (n=91)	81 mg daily: 82 (90) 325 mg daily: 7 (8) Unsure of dose: 2 (2)	Secondary prevention (n=27)	81 mg daily: 24 (89) 325 mg daily: 2 (7) Unsure of dose: 1 (4)
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Secondary prevention (n=27)	81 mg daily: 24 (89) 325 mg daily: 2 (7) Unsure of dose: 1 (4)					

\*Unless otherwise indicated

†Proportion of subjects using aspirin for prevention of cardiovascular events

dose–response relationship hypothesis generated from pharmacologic evidence has not been tested in a clinical trial. If true, this could have a significant impact on clinical practice.

To quantify the potential implications, we followed the principles of a quality improvement process and measured the current patterns of aspirin use in our target population (45). Our cross-sectional study found that 77% of participants with an indication for secondary prevention were regularly using aspirin, which is consistent with the weighted average rate reported in the literature (73%; range 11% to 100%). We also observed that 65% of participants with an indication for primary prevention were regularly using aspirin, which is higher than the rates reported in the literature (weighted average 27%; range 2% to 57%). More importantly, our survey found that most people (90%) using aspirin for prevention of CV events were taking 81 mg daily, which is consistent with other studies reporting that over 60% of people with diabetes take ≤100 mg daily when using aspirin for the prevention of CV events.

There are several limitations to our cross-sectional survey that should be acknowledged. First, the convenience sampling technique introduces volunteer bias, which may have artificially increased the observed rate of aspirin use.

Second, the design does not allow us to conduct a meaningful exploration of factors that may explain the differences in aspirin use rates. Last, we did not collect information on contraindications to aspirin use (documented allergy or previous gastrointestinal bleed), which would decrease the number of subjects eligible for aspirin use. Despite these limitations, our systematic review of the literature and cross-sectional survey help characterize aspirin use in people with diabetes. Furthermore, involving undergraduate students in the study execution addressed a common challenge in practice research—a perception that research is difficult and could not be part of “normal” practice (11). As Armour and colleagues found, we believe undergraduate students need to see the importance of evidence-based practice and experience how pharmacists can contribute to this knowledge base (11). Our hope is that participation in this study will enable these students and their preceptors to play a role in future studies.

In conclusion, our study identified that about one-quarter of people with diabetes who have an indication for primary prevention and over 70% of those with a history of CV events use aspirin regularly. The most common dose of aspirin taken to prevent CV events is  $\leq 100$  mg daily. Current pharmacological and clinical trial evidence would suggest this dose is suboptimal.

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