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Original Article

Impact of Vanessa's Law on the Reporting of Serious Adverse Events: A Retrospective Study Among Antiplatelet Users in a Tertiary-Care Cardiology Centre

Laura Blonde Guefack Djiokeng, BSc,[a,b] Shweta Todkar, RN, PhD,[b,c] Sonia Corbin, RN, BSc,[b,c] Maude Lavallée, RN, MSc,[b,c] Pallavi Pradhan, MSc,[a,b] Magalie Thibault, BA, MSc,[b] Marie-Eve Piché, MD, PhD,[b,d] Julie Méthot, BPharm, PhD,[b,c] Anick Bérard, PhD,[e,f] Jennifer Midiani Gonella, RN, PhD,[g] Fernanda Raphael Escobar Gimenes, RN, PhD,[g] Rosalie Darveau, PharmD, MSc,[b] Isabelle Cloutier, BPharm, MSc,[b,c] and Jacinthe Leclerc, RN, PhD[b,c,h]

[a] *Department of Anatomy, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada*

[b] *Institut universitaire de cardiologie et de pneumologie de Québec—Université Laval, Québec, Québec, Canada*

[c] *Faculty of Pharmacy, Université Laval, Québec, Québec, Canada*

[d] *Faculty of Medicine, Université Laval, Québec, Québec, Canada*

[e] *Faculty of Pharmacy, Université de Montréal, Montréal, Québec, Canada*

[f] *Centre hospitalier universitaire Ste-Justine, Research Centre, Montréal, Québec, Canada*

[g] *Department of General and Specialized Nursing, University of Sao Paulo at Ribeirao Preto College of Nursing, Sao Paulo, Sao Paulo, Brazil*

[h] *Department of Nursing, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada*

ABSTRACT

Background: Antiplatelet drugs, such as clopidogrel, ticagrelor, prasugrel, and acetylsalicylic acid, may be associated with a risk of adverse events (AEs). Vanessa's Law was enacted to strengthen regulations to protect Canadians from drug-related side effects (with mandatory reporting of serious adverse events [SAEs]).

Objective: To determine whether Vanessa's Law has led to an increase in SAE reporting among antiplatelet users.

Methods: This descriptive retrospective study was conducted from January, 2018-December, 2021. Included are 260 adult antiplatelet users (cohorts: 2018 [n = 64]; 2019 [n = 79]; 2020 [n = 73]; 2021

RÉSUMÉ

Contexte : Les médicaments antiplaquettaires, tels que le clopidogrel, le ticagrelor, le prasugrel et l'acide acétylsalicylique, peuvent être associés à un risque d'événements indésirables (EI). La loi de Vanessa a été promulguée pour renforcer la réglementation visant à protéger les Canadiens des effets secondaires liés aux médicaments (avec déclaration obligatoire des événements indésirables graves [EIG]).

Objectif : Déterminer si la loi de Vanessa a entraîné une augmentation des déclarations d'EIG chez les utilisateurs d'antiplaquettaires.

Méthodes : Cette étude rétrospective descriptive a été menée de janvier 2018 à décembre 2021. Ont été inclus : 260 adultes uti-

Pharmacovigilance is a scientific discipline that aims at evaluating, comprehending, and preventing adverse events (AEs) associated with medicinal products.[1-3] An AE is defined as "any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily require to show a causal relationship with the product."[4] AEs constitute one of the main causes of hospitalization in developed countries,[5] with a documented rate of AE-related hospitalization of 8.5 %.[6] Serious AEs (SAEs) are defined by criteria such as inpatient hospitalization, death, life-threatening situations, permanent functional impairment, and congenital anomalies.[4,7]

In Canada, 4 antiplatelet drugs (clopidogrel, ticagrelor, prasugrel, and acetylsalicylic acid [ASA]) are used mainly in the secondary prevention of ischemic vascular events among

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Corresponding author: Jacinthe Leclerc, RN, PhD, FAHA, Institut Universitaire de Cardiologie et de Pneumologie de Québec - Université Laval, 2725 Chemin Sainte-Foy, Québec, Québec G1V 4G5, Canada.

E-mail: jacinthe.leclerc@criucpq.ulaval.ca

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[n = 44]) hospitalized at the Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval. The main diagnostic of hospitalization was coded using the International Classification of Diseases,10th revision, Canadian version, and data related to demographic characteristics, hospitalization length-of-stay, drugs administered, and AEs were extracted.

Results: The 260 antiplatelet users were hospitalized mainly for diseases of the circulatory system (codes [I00-I99]; 2018, 75 %; 2019, 71 %; 2020, 71 %; 2021, 77 %) or diseases of the respiratory system (codes [J00-J99]; 2018, 6 %; 2019, 8 %; 2020, 4 %; 2021, 7 %). The median age was 70 years. The median duration of hospital stay was 3 days. Among the 1395 AEs recorded during the study, 12 % were SAEs. None of the SAEs (or AEs) was reported to Health Canada, either before or after Vanessa's Law implementation.

Conclusions: These results provide the first picture of reporting trends for SAEs among antiplatelet users in Canada. Investigation of the underreporting of SAEs is needed, as the implementation of a mandatory policy does not seem to have had a favourable impact.

Clinical Trial Registration: 135263.

lisateurs d'antiplaquettaires (cohortes : 2018 [n = 64]; 2019 [n = 79]; 2020 [n = 73]; 2021 [n = 44]) hospitalisés à l'Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval. Le diagnostic principal de l'hospitalisation a été codé à l'aide de la Classification internationale des maladies, 10e révision, version canadienne, et les données relatives aux caractéristiques démographiques, à la durée de l'hospitalisation, aux médicaments administrés et aux EI ont été extraites.

Résultats : Les 260 utilisateurs d'antiplaquettaires ont été hospitalisés principalement pour des maladies de l'appareil circulatoire (codes [I00-I99]; 2018, 75 %; 2019, 71 %; 2020, 71 %; 2021, 77 %) ou des maladies de l'appareil respiratoire (codes [J00-J99]; 2018, 6 %; 2019, 8 %; 2020, 4 %; 2021, 7 %). L'âge médian était de 70 ans. La durée médiane du séjour à l'hôpital était de 3 jours. Parmi les 1395 EI enregistrés au cours de l'étude, 12 % étaient des EIG. Aucun EIG (ou EI) n'a été signalé à Santé Canada, que ce soit avant ou après la loi de Vanessa.

Conclusions : Ces résultats fournissent la première image des tendances en matière de déclaration des EIG parmi les utilisateurs d'antiplaquettaires au Canada. Une enquête sur la sous-déclaration des EIG est nécessaire, car la mise en œuvre d'une politique obligatoire ne semble pas avoir eu un impact favorable.

Enregistrement de l'essai clinique : 135263.

patients with atherosclerosis, nonhemorrhagic strokes, and acute coronary syndromes (unstable angina and myocardial infarction).[8,9] These antiplatelet agents may be the cause of severe SAEs, such as hemorrhage, which potentially is fatal.[9,10] An alarming finding is that, reportedly, only 5 % of AEs are communicated to health authorities, raising concerns about monitoring and reporting practices in Canada.[11]

The tragic death of 15-year-old Vanessa Young in 2000 due to a drug-related cardiac arrhythmia prompted legislative action.[12] This death, like many others, might have been avoided if the SAEs associated with this drug had been reported duly to the health authorities. Vanessa's Law, implemented in 2019, mandates that healthcare institutions report SAEs to Health Canada through the MedEffect platform of the Canada Vigilance Program, aiming to enhance drug safety and improve public health.[12,13]

The objective of this study was to assess the impact of Vanessa's Law on the reporting of SAEs among antiplatelet-drug users in a tertiary-care cardiology centre. We hypothesized that the reporting rates of SAEs would increase after, vs before, the implementation of Vanessa's Law. This study also explored the effect of the type of antiplatelet used on SAEs reporting trends.

Method

Study design and period

This descriptive, retrospective study was carried out over a period of 4 years, from January 2018 to December 2021. This period covers the 24 months preceding, and the 24 months following, the implementation of Vanessa's Law in Canada, as recommended for this type of design.[14,15]

Target population and settings

Adult antiplatelet users hospitalized at the Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval (IUCPQ-ULaval) were the target population. The IUCPQ-ULaval is a 338-bed tertiary academic hospital that provides specialized care for patients with cardiovascular, pulmonary, and metabolic diseases.[16]

Eligibility criteria

All adult patients hospitalized at the IUCPQ-ULaval during the study period and who had taken one or more antiplatelet drugs were eligible. The only exclusion criteria for a patient were as follows: (i) having not received antiplatelet medications during their hospitalization; and (ii) having participated in a double-blind randomized clinical trial, for which it would not be possible to collect data on all the drugs received during the episode of care.

Sample size and selection

This study was a pilot project of a larger study. Therefore, among a database of 500 patients randomly selected by an IUCPQ-ULaval archivist (125 patients in each annual cohort, regardless of drug class, giving a total of 500 patients for the 4 cohorts [2018-2021]), patients who had taken $\geq$ 1 antiplatelet agent were included. This approach provided a sample of 260 patients for this study, distributed as follows: 64, 79, 73, and 44, for the 2018, 2019, 2020, and 2021 cohorts, respectively.

Data source and extraction

The entire episode of care of the selected patients was investigated from their electronic medical records (EMRs),

hosted on the Cristal-Net platform.[17] The following data were extracted from EMRs into an anonymized research database hosted on the Research Electronic Data Capture (REDCap) platform.

Demographic data. The date of birth and the sex of patients were collected in the form in which they were written in the EMR. We calculated the patients' age using their date of birth.

Hospitalization-related data. The reasons for justifying the hospital stay were coded with the International Classification of Diseases, 10th revision, Canadian version (ICD-10-CA), by IUCPQ-ULaval's archivist. The dates of admission and discharge were extracted from the EMR and were used to calculate the length of hospital stay.

Pharmaceutical products—related data. Pharmaceutical medications received during the stay were recorded using generic names, including all the medications administered by nurses, anesthesiologists, respiratory therapists, etc.

AE-related data. Incident AEs were extracted from the EMR and coded with the Medical Dictionary for Regulatory Activities (MedDRA).[18] Among the MedDRA hierarchy, the system organ class was used for categorization. AEs were considered serious (SAEs) if they met the criteria of the Health Canada definition.[19] An AE is defined as a noxious and unintended reaction to a drug, which does not need to have a cause-and-effect relationship with the drug treatment.[19,20] In cases in which a cause-and-effect relationship is established, it is defined as an adverse drug reaction or side effect.[19] An important point to note is that AEs may be considered a side effect, but not all side effects are AEs.[19] The study of adverse drug reactions with proven causality was outside the scope of the current study. A point of note that should be emphasized is that a formal causality assessment is not required for reporting of AEs or SAEs to Health Canada.[19]

Exposure

The implementation of Vanessa's Law constitutes the main ecological exposure for this study. Even though the exposure remains ecological in nature, a point to note is that at the IUCPQ-ULaval, to promote compliance with Vanessa's Law requirements, organized training for healthcare professionals was conducted before the implementation of the law. Another point of note is that training was not part of this retrospective observational study. In addition, a process involving the pharmacy and the archive department has been established to maximize the chances of SAEs being reported to Health Canada. At IUCPQ-ULaval, the internal procedure requires use of a specific form (CP5988) when an AE and/or an SAE related to a drug occurs. Once the form is completed, it is scanned into the patient's EMR and submitted to Health Canada. A register of these forms is available in the pharmacy department of IUCPQ-ULaval via the "Loi de Vanessa" (Vanessa's law) registry.[21] The AE and/or SAE was considered to have been reported to Health Canada if we found a completed CP5988 form documenting it, or if the AE and/or SAE report was mentioned in the EMR.

Outcome

The main outcomes were the reporting of SAEs that occured after antiplatelet use, and their reporting to Health Canada by IUCPQ-ULaval's healthcare professionals.

Statistical analysis

We first extracted from the initial 500 patients all those who had taken $\geq$ 1 antiplatelet agent during their hospital stay (Table 1). Descriptive analyses were performed to characterize the study sample (median, minimum—maximum, proportion; Table 2; Supplemental Table S1). We calculated the total number of SAEs, and subsequently, the annual SAE reporting rate (Table 3). The SAE reporting rate was calculated as follows: ([number of SAEs reported/number of SAEs] *100). To quantify the change in SAE reporting rates after vs before the implementation of Vanessa's Law, segmented regression models were planned a priori with the following 4 segments: (i) the period before implementation of the law (January 1, 2018-December 15, 2019); (ii) the period during implementation of the law (December 16, 2019-January 15, 2020); (iii) the period after implementation of the law (January 16, 2020-March 15, 2020); and finally, (iv) the COVID-19 pandemic period (March 16, 2020-December 31, 2021). Stratifications also were planned a priori, according to the type of antiplatelet agent, age, sex, and year. To assess whether continuous data were normally distributed, the Kolmogorov—Smirnov and Shapiro—Wilk tests were used. Due to the nature of the results, post hoc power estimations also were performed. Analyses were performed with SPSS Statistics for Windows software, version 29.0 (IBM, Armonk, NY). We used the Research Electronic Data Capture (REDCap) platform, which interfaces seamlessly with SPSS, enabling direct data export.

Ethical considerations

Anonymity was always preserved; the data were coded. Ethics approval was obtained from the ethics committees of the IUCPQ-ULaval research centre and the Université du Québec à Trois-Rivières. As obtaining informed consent was not feasible in the context of this study, the Director of Professional Services of IUCPQ-ULaval provided authorization to access the EMRs.

Results

Proportion of antiplatelet drugs registered by annual cohort

Table 1 reports the distribution of antiplatelet and non-antiplatelet users through the cohorts (2018-2021). Depending on the cohorts, antiplatelet users selected for this

Table 1. Distribution of antiplatelet and nonantiplatelet users

Cohorts, by year	2018	2019	2020	2021	Total
Antiplatelet	64 (51)	79 (63)	73 (58)	44 (35)	260 (52)
Nonantiplatelet	61 (49)	46 (37)	52 (42)	81 (65)	240 (48)
n	125	125	125	125	500

Values are n (%), or n.

Table 2. Descriptive analyses for sample characterization

Variables	n = 260
Demographic characteristics	
Age, y	70 (21−96; 15)
0−64	79 (30)
≥ 65	181 (70)
Sex	
Male	167 (64)
Female	93 (36)
Hospitalization	
Reason (ICD-10-CA codes)	
Circulatory system diseases (I00−I99)	190 (73)
Respiratory system diseases (J00−J99)	16 (7)
Duration, d	3 (1−15; 4)
Death during stay	3 (1)
COVID-19 diagnosis	2
Pharmaceutical products	
Total	5364
Taken per patient	19 (4−53; 10)
AE and SAE characteristics	
Total AEs	1395
Number of AEs per patient	4 (0−26; 6)
Total SAEs	166
Number of SAEs per patient	0 (0−7; 1)
Proportion of SAEs among all AEs, %	12

Values are median (minimum−maximum; interquartile range), n (%), or n, unless otherwise indicated.

AE, adverse event; ICD-10-CA, International Classification of Diseases, 10th revision, Canadian version; SAE: serious AE.

study (n = 260) represented 35 % to 63 % of the initial randomly selected cohort of 500 participants. Table 4 shows that the 260 patients took 380 antiplatelet medications over the study period, due to the overlapping nature of the combination therapy in some patients. The most frequently used antiplatelet drug was ASA (n = 247; 65 %), followed by clopidogrel (n = 107; 28 %), and ticagrelor (n = 26; 7 %). No patient received prasugrel in our study sample. Prasugrel was not available in Canada between February 2020 and July 2021, and it was available only through the Health Canada's special access programs for users who were unable to receive ticagrelor or clopidogrel in combination with ASA.[22] Supplemental Table S2 shows that the most frequent combination therapy was ASA and clopidogrel (n = 93). A total of 117 of 260 patients (45 %) received a combination therapy (Supplemental Table S3).

Patients' characteristics

As shown in Table 2, patients predominantly were aged > 65 years (70 %) and were of male sex (64 %). The main cause of hospitalization, per the ICD-10-CA coding, was diseases of the circulatory system (ICD-10-CA codes I00-I99; 73 %). The median age of patients was 70 years (minimum−maximum [min−max], 21-96 years), and the median length of hospital stay was 3 days (min−max, 1-15 days).

Table 3. Adverse event (AE) and serious AE (SAE) reporting rate

Cohorts	2018	2019	2020	2021
Reported to Health Canada				
SAEs	0 (0)	0 (0)	0 (0)	0 (0)
AEs	0 (0)	0 (0)	0 (0)	0 (0)

Table 4. Distribution of frequency and proportion of antiplatelet drugs

Cohorts, by year	2018	2019	2020	2021	Total
ASA	58 (24)	78 (32)	70 (28)	41 (17)	247 (65)
Clopidogrel	30 (28)	29 (27)	33 (31)	15 (14)	107 (28)
Ticagrelor	5 (19)	7 (27)	9 (35)	5 (19)	26 (7)
Prasugrel	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total n	93	114	112	61	380

Values are n (%), or n. Note: n = 260; total may vary due to combination therapy (n = 380). ASA, acetylsalicylic acid.

Incident AEs in patients taking antiplatelet agents

Table 2 shows that 1395 AEs were recorded, and a median of 4 AEs (min−max, 0-26) per patient. Of the AEs recorded, 166 met seriousness criteria (ie, were SAEs). Three deaths occurred during hospitalization, and a total of 236 patients had ≥ 1 AE. Using the MedDRA coding system, we have listed the 10 most frequently encountered AEs (Fig. 1), and listed all AEs (Supplemental Table S4) and SAEs (Supplemental Table S5; Supplemental Fig. S1). The most-frequent incident AEs concern cardiac disorders (20 %; Fig. 1). Figure 2 shows the distribution of AEs recorded by the type of antiplatelet agent. Furthermore, 66 % of AEs were recorded in patients who had received ASA during hospitalization; 27 % were recorded in those who had received clopidogrel; and 7 % were recorded in those who had received ticagrelor.

A 1-way analysis of variance was conducted to compare the rate of AEs for the single-therapy vs the combination-therapy groups. Comparisons were made among the single-therapy group and the combination-therapy groups (these include the following: ASA, clopidogrel, ticagrelor vs ASA + clopidogrel; ASA + ticagrelor; clopidogrel + ticagrelor; ASA and/or clopidogrel and/or ticagrelor). No significant difference occurred in the rate of AEs between the groups: F-value (1, 258) = 0.035; $P = 0.852$. The results revealed that the rate of AEs was similar across all groups. Specifically, the mean rate of AEs for the single-therapy groups was M = 5.42 (standard deviation = 5.449), and for the combination-therapy groups, it was M = 5.30 (standard deviation = 4.836). Post hoc comparisons were not conducted, as the overall analysis of variance results were not significant.

Reporting of SAEs to Health Canada

As shown in Table 3, none (0 %) of the SAEs or AEs were reported to Health Canada, either before or after the implementation of Vanessa's Law. A post hoc power estimate revealed that for each cohort, the study power varied from 94 % (in 2021; n = 44) to 98 % (in 2019; n = 80). As we observed a null proportion of SAEs reported to Health Canada, the other a priori planned analyses (segmented regression models and stratification) could not be performed.

Discussion

This retrospective study identified 1395 in-hospital AEs, 12 % of which were SAEs. None of these AEs were reported to Health Canada, challenging the assumed positive impact of Vanessa's Law on SAE reporting for antiplatelet drugs. These results contradict the initial hypothesis and aligns with international findings indicating that only 5 % of AEs are

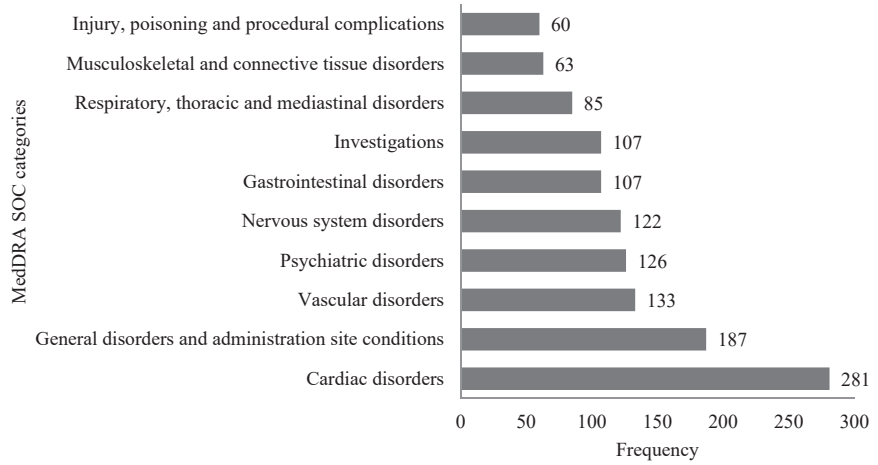

Figure 1. List of top-10 recorded adverse events (AEs), coded per the medical dictionary for regulatory activities, system organ class (MedDRA SOC) categories. Frequency represents the number of AEs recorded for each SOC. Total number of AEs was recorded; n = 1395.

reported to health authorities.[11] To our knowledge, this study is the first addressing the reporting of SAEs, before and after the implementation of a mandatory SAE reporting policy regarding the antiplatelet class of drugs.

Underreporting of SAEs, before and after implementation of Vanessa's Law

Although the initial hypothesis has not been confirmed by these data, the observed underreporting of AEs is in line with the results of an international systematic review that found that < 5 % of AEs are reported to the health authorities.[11] Similarly, another study carried out in 5 hospitals in Norrbotten in Sweden showed an underreporting rate as high as 86 %—that is, 14 % of reports.[23] Despite efforts made at the IUCPQ-ULaval to comply with Vanessa's Law, our study detected no reported SAEs, raising questions about the law's effectiveness. After we obtained our results, we asked the IUCPQ-ULaval if it would grant us access to the registry "Loi de Vanessa," with all the AE and/or SAE reports (CP5988) made to Health Canada. A total of 76 reports were included in the registry from December 16, 2019-December 31, 2021. Annually, the IUCPQ-ULaval records approximately 16,000 hospitalizations; the AE and/or SAE reports represent a proportion of 0.001 %. However, none of the AE and/or SAE data collected, or those of the 500 patients in our study, were part of the registry. Post hoc power calculations suggest that the study had sufficient power (≥ 94 %), emphasizing the pervasiveness of underreporting of SAEs and AEs to Health Canada.

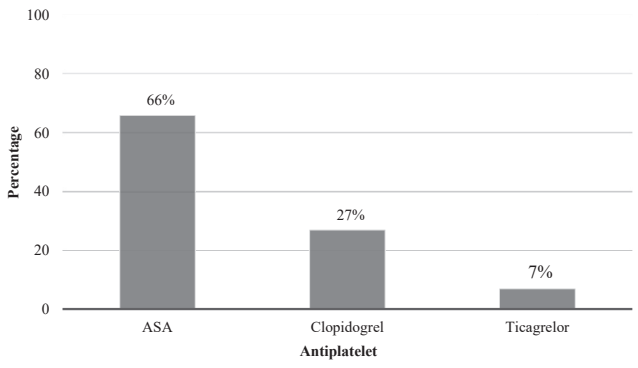

Figure 2. Proportion of adverse events (AEs) recorded by type of antiplatelet drug. Total number of AEs was recorded for individual antiplatelet drug; n = 2022. The discrepancy observed for not reaching the total AE count of 1395 is due to the overlapping nature of the combination therapy. ASA, acetylsalicylic acid.

Reporting trends for AEs among antiplatelet-drug users

Making comparisons with existing literature is challenging, due to the lack of similar studies. Some studies have dealt solely with AEs associated with antiplatelet-drug use.[24,25] In 2018, the US Food & Drug Administration's AE reporting system study on 3 antiplatelet drugs showed that cardiovascular issues were the most common AEs, consistent with our findings of a predominance in cardiovascular disorders.[24] The study also showed that cardiovascular problems were the most frequently encountered AEs for all 3 antiplatelet agents that is, approximately 5398 cardiovascular issues.[24] This same study also had a predominance of cardiovascular disorders (n = 281), with an incidence of AEs similar to the level we observed in our study sample. The AEs and/or SAEs identified in our study were not necessarily caused solely by use of antiplatelet drugs or other medications. Some of the AEs and/or SAEs observed in the cohort can be attributed to underlying pathologies, complications related to the primary reason for admission, new diagnoses, use of other medications, drug—drug interactions, and several other factors.[4] Also, the assessment of causality—that is, establishing a diagnosis of an AE being associated with drug use—was beyond the scope of this study.

Causes of underreporting

The underreporting of AEs to Health Canada under Vanessa's Law raises concerns. Potential causes include healthcare professionals' lack of awareness, and constraints on their time.[26,27] This issue also could be linked to a lack of knowledge on the part of professionals.[26,28] Even though training was offered before the implementation of Vanessa's

Law, healthcare professionals may not have attended the training, and they may not know about the obligation for healthcare institutions to report SAEs. In the hospital environment, healthcare professionals (especially physicians and nurses) very often are overworked, so this underreporting also could be linked to a lack of time available to report AEs. Some studies reported that the main factors causing underreporting were the lack of seriousness of the AE, the fact that the AE was an already-known side effect, uncertainty as to the causal link between the AE and a drug, forgetting to report the AE, and lack of time.[27,29] Addressing these barriers is crucial for improving the level of AE reporting and the understanding of the real-world benefits and risks of various drugs.

Strengths and limitations

This retrospective descriptive study, although is is methodologically rigorous and presents novel findings, has limitations. The analysis focused on a specific subgroup of patients who used antiplatelet medications, and this focus may limit the generalizability of the results to a broader population. Additionally, these data come from a single specialized tertiary-care centre, a situation that may affect the generalizability of the results to all hospitals in Canada. The risk of information bias was minimized through standardized data extraction and validation processes. Moreover, we had full access to records regarding the patient's hospital stay (medical notes, laboratory results, medication administration forms, etc.). However, the use of hospitalization forms for recording comorbidities can introduce limits in this type of analysis, owing to potential inaccuracies or inconsistencies in the recorded data.

Implications

Given the study population's vulnerability (70 % aged $\geq$ 65 years), and the observed incidence of AEs, the level of AE underreporting is concerning. A study in Portugal reported a 34 % hospitalization rate, and a 5.8 % fatality rate, among people aged $>$ 65 years who experience AEs, emphasizing the importance of pharmacovigilance reporting in this demographic.[30] However, this study also showed that 13.6 % of these AEs were linked to use of antithrombotic drugs, the class of drugs to which antiplatelet agents belong. Pharmacovigilance reporting of AEs that occur among the elderly is necessary to enable large-scale epidemiologic studies, as well as better identification of iatrogenic risk factors.[31]

Conclusion

Vanessa's Law appears to have little impact on SAE reporting relating to antiplatelet-drug use in this study. Further research is needed to uncover the causes of underreporting and develop solutions for it, thereby ensuring more-robust SAE reporting, and ultimately, enhancing drug-use safety.

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Ethics Statement

Anonymity always was preserved; the data were coded. The research presented in this document complies with the Helsinki ethical principles and has been approved by the Ethics Committee of the IUCPQ-ULaval and the Université du Québec à Trois-Rivières. As obtaining informed consent was not feasible in the context of this study, the Director of Professional Services of the IUCPQ-ULaval provided authorization to access the EMRs.

Patient Consent

The authors confirm that patient consent is not applicable to this article. For this retrospective study, obtaining informed consent by each patient was not feasible; the Director of Professional Services of the IUCPQ-ULaval provided authorization to access the EMRs of the participants.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.09.003.