Appropriateness of Ticagrelor Use at Initiation: A Population-Based Cohort Study

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ABSTRACT - Purpose. Ticagrelor is recommended following an acute coronary syndrome if used appropriately. Its use has not yet been well described in the context of ambulatory clinical practice. The objective of this study was to assess the proportion of ticagrelor new users who initiated this medication appropriately and explore associated factors. **Methods**. A retrospective population-based inception cohort study was conducted using Quebec administrative databases. The study population included all Quebec residents aged ≥18 years who had a first ticagrelor prescription claim between 1 January, 2012, and 31 March, 2015, and had been continuously eligible in the Quebec public drug plan during the 365 days preceding the first ticagrelor claim. The initial ticagrelor prescription was considered appropriate if:1) it met the indication for use criterion, 2) the prescribed daily dose was 90 mg twice a day, and 3) there was a concomitant use of acetylsalicylic acid (ASA) 80–81 mg daily. Factors potentially associated with the ticagrelor appropriateness of use were included in a logistic log-binomial regression model. **Results**. A total of 7,073 patients were included in the study, 6,013 (85.0%) had an appropriate indication, 6,895 (97.5%) were prescribed ticagrelor 90 mg twice a day, and 6,385 (90.3%) had a concomitant prescription of ASA. A total of 5,371 (75.9%) patients were prescribed ticagrelor in accordance with all criteria. Twelve factors were associated with prescription appropriateness. **Conclusions**. A large majority of patients initiated ticagrelor appropriately. Further improvement in appropriateness may come at targeting indication for use.

INTRODUCTION

Acute coronary syndrome (ACS) includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).[1] Secondary prevention medication is critical regarding the reduction of cardiovascular adverse events and death in the years following an ACS. Since 2011, the antiplatelet drug ticagrelor has been available in Canada. When co-administered with low doses of acetylsalicylic acid (ASA), this selective adenosine diphosphate receptor antagonist is indicated in the secondary prevention of ACS.[2] In 2013, the Canadian Cardiovascular Society (CCS) updated guidelines regarding the use of antiplatelet therapy, including the use of ticagrelor.[3]

The prescription of adenosine diphosphate receptor antagonists including ticagrelor has been assessed using selected data from hospital settings.[4 5 6 7] However, to our knowledge it has not yet been well described in the context of an ambulatory clinical practice using population-based data. In addition, factors associated with the appropriate use of ticagrelor remain unstudied. As ticagrelor has been available for reimbursement through the province of Quebec public drug plan since February 2012, data from the Quebec Health Insurance Board (RAMQ) provided the opportunity to evaluate the ambulatory use of ticagrelor within the drug plan. This medico-administrative study was conducted to assess the proportion of ticagrelor new users who appropriately initiated this drug, and to explore factors associated with appropriate use.

METHODS

Study Design and Data Source

This retrospective population-based inception cohort study was conducted using databases from the RAMQ and the Quebec registry of hospitalizations. These databases include information on patient demographics, hospitalization, and physician services pertaining to all permanent residents of the province of Quebec. The RAMQ pharmaceutical services database also contains information on prescription drugs for all beneficiaries of the provincial public

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drug plan (Quebec residents who are not eligible for a private drug insurance plan, welfare recipients, and people aged ≥ 65 years).

Population

All Quebec residents aged ≥ 18 years who had at least one claim of ticagrelor in the RAMQ pharmaceutical services database between 1 January, 2012, and 31 March, 2015 were included. They also had to have continuous eligibility in the Quebec public drug plan during the 365 days preceding their first ticagrelor claim.

Variables

The appropriateness of the first ticagrelor prescription claimed was evaluated considering 3 criteria based on the CCS updated guidelines regarding the use of antiplatelet therapy:[3] 1) indication for use, 2) ticagrelor daily dose, and 3) concomitant prescription of ASA 80–81 mg daily. A patient was considered to have an appropriate indication if in the 365 days before or at the date of the first ticagrelor claim there was a diagnosis of ACS with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). An ACS diagnosis without PCI or CABG was also considered appropriate if the patient was ≥ 60 years or had an ischemic stroke, diabetes, peripheral arterial disease, or chronic renal dysfunction.[3] A ticagrelor daily dose was considered appropriate if it was 90 mg twice daily, and a patient was considered to be taking concomitant ASA if dispensed enough units of ASA 80–81 mg to be covered at the date of the first ticagrelor claim. The ticagrelor and the ASA daily doses were assessed using the dosage, the quantity dispensed, and the number of days supplied.

An array of patient-related, health-related, and treatment-related characteristics were considered as factors potentially associated with the ticagrelor appropriateness of use. Patient-related characteristics were assessed at the date of the first ticagrelor claim. They included age, sex and socioeconomic status (no/partial/maximum guaranteed income supplement). The following health-related characteristics were assessed in the year before the first ticagrelor claim (date of first ticagrelor claim included) using physician services or hospital data: presence of cardiac-related diseases and other comorbidities (diabetes, hypertension, dyslipidemia, ischemic stroke, peripheral arterial disease), chronic renal dysfunction, upper gastro-intestinal bleeding, and diseases that may reduce life expectancy (dementia, non-skin neoplasia). As for the treatment-related characteristics, the specialty of the physician who initially prescribed ticagrelor and the calendar year of treatment initiation were assessed. Health services characteristics were also assessed in the year preceding the date (included) of the first ticagrelor claim: total number of days of hospitalization; total number of physician visits; visits to a general practitioner (yes/no) and to a cardiologist (yes/no); cardiac revascularization procedures (CABG, PCI); and drugs (number of distinct drugs claimed, cardiovascular drugs).

STATISTICAL ANALYSIS

The proportion of patients who used ticagrelor appropriately was calculated. Patient characteristics were assessed using descriptive statistics. Factors that were potentially associated with appropriate prescription were explored using a multivariable log-binomial regression model. Using the stepwise procedure, all variables with a *P*-value <0.05 were kept in the model. Adjusted prevalence ratios (PR) with 95% confidence intervals (CIs) were calculated. Factors were considered to be associated with the appropriateness of ticagrelor use if the adjusted PR was statistically significant, i.e. if the 95% CI did not include the '1' value (alternatively if the P-value was < 0.05). There was no issue of multicollinearity, which was assessed using a multiple regression analysis. Analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Ethics

The study research protocol was approved by the Research Ethics Committee of the *CHU de Québec-Université Laval* Hospital.

RESULTS

A total of 7,073 patients undertaking a ticagrelor regimen constituted the study population. Of these patients, 6,013 (85.0%) had an appropriate indication, 6,895 (97.5%) were prescribed ticagrelor 90 mg twice a day, and 6,385 (90.3%) had a concomitant prescription of ASA at a dosage of 80–81 mg (Table 1). A total of 190 (2.7%) patients had no ASA claim. In all, 5,371 (75.9%) individuals initiated ticagrelor appropriately, i.e. in accordance with all of the aforementioned criteria. The mean (standard deviation) age of the patients was 67.8 (10.7) years, with 5,585 (78.9%) patients aged ≥ 60 years. A total of 4,738 (67.0%) patients were men. A high proportion of patients had cardiovascular comorbidities and used cardiovascular drugs. Only 315 (4.5%) had not been hospitalized in the 365-day period preceding their first ticagrelor claim. A total of 1,203 (17.0%) patients had previously used clopidogrel or prasugrel.

Table 1. Ticagrelor appropriate prescription in patients who initiated this drug between January 1, 2012 and March 31, 2015 (n = 7,073)

Criteria for ticagrelor appropriate prescription	*n*	%
Appropriate indication		
Yes	6,013	85.0
No	1060	15.0
(ACS[a] without PCI[b] or CABG[c] and without age ≥ 60 years, ischemic stroke, diabetes, peripheral arterial disease or chronic renal dysfunction)	(153)	(14.4)*
(No ACS)	(907)	(85.6)*
Dosage of the first ticagrelor claim = 90 mg twice a day		
Yes	6,895	97.5
No	178	2.5
(Dosage > 90 mg twice a day)	(87)	(48.9)*
(Dosage < 90 mg twice a day)	(91)	(51.1)*
Concomitant prescription of ASA[d] 80–81 mg		
Yes	6,385	90.3
No	688	9.7
Had a dosage of ASA ≠ 80–81 mg	(498)	(72.4)*
Had no ASA	(190)	(27.6)*
Appropriate prescription (met all criteria)		
Yes	5,371	75.9
No	1,702	24.1
No recommended indication	(904)	(53.1)*
Dosage of the first ticagrelor claim ≠ 90 mg twice a day	(93)	(5.5)*
No ASA 80–81 mg	(488)	(28,7)*
No indication and dosage of the first ticagrelor claim ≠ 90 mg twice a day	(17)	(1,0)*
No indication and no ASA 80–81 mg	(132)	(7,7)*
Dosage of the first ticagrelor claim ≠ 90 mg twice a day and no ASA 80-81 mg	(61)	(3,6)*
No indication, dosage of the first ticagrelor claim ≠ 90 mg twice a day and no ASA 80-81 mg	(7)	(0.4)*

* Denominator: number of patients whose ticagrelor prescription did not meet the criterion
[a] ACS: acute coronary syndrome
[b] PCI: percutaneous coronary intervention
[c] CABG: coronary artery bypass grafting
[d] ASA: acetylsalicylic acid

A total of 12 factors were kept in the final multivariable model. All 12 factors were statistically associated with the appropriate initial use of ticagrelor (Table 2). Patients with prior cardiac dysrhythmia, chronic renal dysfunction, dyslipidemia and hypertension, as well as those who, in the year prior to the initiation of ticagrelor, visited a general practitioner, took a statin or fibrate, and took antihypertensive agents, were more likely to initiate ticagrelor appropriately. On the other hand, the likelihood to use ticagrelor appropriately was reduced among patients who had atrial fibrillation, cardiomyopathy and dyspnea, those who had made more than 6 visits to a physician, and those who had used clopidogrel or prasugrel in the year before initiating ticagrelor.

DISCUSSION

One principal finding emerges from this study. Three out of four individuals initiated ticagrelor according to all criteria of appropriateness. Noteworthy, the proportion of appropriate use with regard to the concomitant use of ASA 80-81 mg was very high (90.3%).

The proportion of appropriateness of use varied according to each of the 3 criteria. The high proportion (85.0%) of appropriateness on indication for use suggests that physicians might have been aware either of the CCS guidelines[3] on that criterion or of the PLATO[8] study inclusion criteria on which the CCS guidelines are based. This proportion is higher than the one observed in a registry study including 227 patients who started ticagrelor at a PCI facility in Saskatchewan.[4] In this latter study, only 67.6% of patients had met the indication criteria, which were similar to ours. As in the current study, a high proportion of individuals (97.5%) were prescribed ticagrelor 90 mg twice daily, which illustrates a close-to-perfect adherence to the daily dose recommended in the CCS guidelines.[3]

Only 190 (2.7%) individuals were not using ASA concomitantly with ticagrelor. Although low, this proportion may have been underestimated as some individuals may have bought their prescribed

ASA over the counter, and therefore, those transactions were not captured in the RAMQ database. In an administrative database study conducted in Denmark including all patients hospitalized for a first myocardial infarction from 2009 through 2012, Green et al.[6] observed that 100% of the 921 patients discharged with ticagrelor were prescribed ASA. In a study conducted in Sweden including patients hospitalized for ACS, 97.8% of patients discharged with ticagrelor were prescribed concomitant use of ASA.[7]

Seven factors associated with ticagrelor appropriateness of use were health-related characteristics (atrial fibrillation, cardiac dysrhythmia, cardiomyopathy, chronic renal dysfunction, dyslipidemia, dyspnea, hypertension), while 5 were treatment-related characteristics (number of physician visits, visits to a general practitioner, prior use of clopidogrel or prasugrel, prior use of a statin or fibrate, and prior use of an antihypertensive drug). The clinical significance of observed associations is difficult to establish as most were weak in magnitude. They are also difficult to interpret in absence of clinical data not captured in the administrative databases. Results should therefore be considered for their exploratory value as they highlight some areas for future research aiming to optimize ticagrelor prescribing practices.

LIMITATIONS

This study has some limitations inherent to the use of administrative databases. First, because prescriptions issued by physicians are not captured in the databases, we were able to assess only prescriptions that were filled at the pharmacy. As mentioned above, ASA may have been prescribed to some patients who chose not to fill their prescription or bought it over the counter. However, the impact of this is likely to be minimal given only 2.7% of patients did not claim an ASA concomitantly to ticagrelor. Second, as it is not mandatory for physicians in Quebec to record all diagnoses when they claim to RAMQ an ambulatory service provided to patients, an unknown proportion of patients prescribed ticagrelor may have had an ACS but this diagnosis was not registered in the 365-day period preceding ticagrelor initiation. This could be the case for some of the 477 patients (data not shown) who had a PCI or a CABG and for whom there was no record of ACS. Therefore, the proportion of appropriate ticagrelor initial use may have been underestimated. Third, many clinical characteristics (ex.: bradycardia, shortness of breath, use of biomarkers) are not captured in the RAMQ administrative database. Therefore, some cases not meeting criteria for appropriateness could have been judged as appropriate if an in-depth assessment of the clinical situation would have been possible. Consequently, cases of non-appropriateness should be considered as "potentially" non-appropriate. Finally, it was not possible to explore some prescriber-related factors (knowledge and attitudes) that could be associated with the quality of prescribing since this information is not recorded.

CONCLUSIONS

In this study, the appropriateness of ticagrelor use at initiation of treatment was assessed in the context of ambulatory clinical practice. It had not yet been done using population-based data. Our results suggest that overall, this medication was appropriately used by a majority of patients. Identified associated factors might help better understand why some patients are potentially using ticagrelor non-appropriately.

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ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

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Table 2. Association between patient-related, health-related and treatment-related characteristics and ticagrelor appropriate prescription (*n* = 7,073)

Characteristics	Appropriate use				Crude Prevalence Ratio (PR)	95% Confidence intervals	*P* value	Adjusted PR	95% Confidence intervals	*P* value
	Yes		No							
	n 5,371	(%) (75.9)	*n* 1,702	(%) (24.1)						
Patient-related										
Age, mean ± standard deviation	67.8±10.7		67.6±10.7		1.00	0.99-1.01	0.87			
Sex										
Women	1,761	32.8	574	33.7	1.00					
Men	3,610	67.2	1128	66.3	1.01	0.98-1.04	0.48			
Socioeconomic status										
No Guaranteed Income Supplement (GIS)	3,156	58.8	998	58.6	1.00					
Partial GIS	1,553	28.9	480	28.2	1.01	0.98-1.04	0.63			
Welfare or maximum GIS	662	12.3	224	13.2	0.98	0.94-1.03	0.72			
Calendar year at ticagrelor initiation										
2012	488	9.1	148	8.7	1.00					
2013	1,805	33.6	596	35.0	0.98	0.93-1.03	0.74			
2014	2,417	45.0	756	44.4	0.99	0.95-1.04	0.76			
2015	661	12.3	202	11.8	1.00	0.94-1.06	0.95			
Health-related										
Anemia										
No	4,493	83.6	1,445	84.9	1.00	0.99-1.06	0.21			
Yes	878	16.4	257	15.1	1.02	0.99-1.06	0.21			
Atrial fibrillation										
No	4,980	92.7	1,566	92.0	1.00			Ref		
Yes	391	7.3	136	8.0	0.98	0.93-1.03	0.35	0.94	0.89-0.98	0.01
Cardiac dysrhythmia										
No	3,831	71.3	1,290	75.8	1.00			Ref		
Yes	1,540	28.7	412	24.2	1.05	1.03-1.08	<0.01	1.07	1.04-1.10	<0.01
Cardiomyopathy										
No	5,243	97.6	1,634	96.0	1.00			Ref		
Yes	128	2.4	68	4.0	0.86	0.77-0.95	<0.01	0.89	0.80-0.98	0.02
Chronic heart failure										
No	4,315	80.3	1,352	79.04	1.00					
Yes	1,056	19.7	350	20.6	0.99	0.95-1.02	0.42			

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Characteristics	Appropriate use				Crude Prevalence Ratio (PR)	95% Confidence intervals	*P* value	Adjusted PR	95% Confidence intervals	*P* value
	Yes		No							
	n 5,371	(%) (75.9)	*n* 1,702	(%) (24.1)						
Chronic renal dysfunction										
No	4,652	86.6	1,512	88.8	1.00			Ref		
Yes	719	13.4	190	11.2	1.05	1.01-1.09	0.01	1.06	1.03-1.10	<0.01
Chronic obstructive pulmonary disease										
No	4,639	86.4	1,473	86.5	1.00					
Yes	732	13.6	229	13.5	1.00	0.97-1.04	0.85			
Deep venous thrombosis										
No	5,360	99.8	1,698	99.8	1.00					
Yes	11	0.2	4	0.2	0.97	0.71-1.31	0.82			
Dementia										
No	5,263	98.0	1,668	98.0	1.00					
Yes	108	2.0	34	2.0	1.00	0.91-1.10	0.97			
Diabetes										
No	3,638	67.7	1,144	67.2	1.00					
Yes	1,733	32.3	558	32.8	0.99	0.97-1.02	0.69			
Dyslipidemia										
No	1,603	29.9	692	40,7	1.00			Ref		
Yes	3,768	70.1	1110	59.3	1.13	1.10-1.16	<0.01	1.09	1.05-1.12	<0.01
Dyspnea										
No	4,718	87.8	1,411	82.9	1.00			Ref		
Yes	653	12.2	291	17.1	0.90	0.86-0.94	<0.01	0.93	0.89-0.97	<0.01
Hypertension										
No	1,763	32.8	660	38.8	1.00			Ref		
Yes	3,608	67.2	1042	61.2	1.07	1.04-1.10	<0.01	1.03	1.00-1.06	0.04
Ischemic stroke										
No	5,121	95.3	1,608	94.5	1.00					
Yes	250	4.7	94	5.5	0.95	0.89-1.02	0.17			
Non-skin neoplasia										
No	4,514	84.0	1,425	83.7	1.00					
Yes	857	16.0	277	16.3	0.99	0.96-1.03	0.76			
Peptic ulcer										
No	5,324	99.1	1,677	98.5	1.00					
Yes	47	0.9	25	1.5	0.86	0.72-1.02	0.08			

Table 2. Association between patient-related, health-related and treatment-related characteristics and ticagrelor appropriate prescription (*n* = 7,073)

Characteristics	Appropriate use				Crude Prevalence Ratio (PR)	95% Confidence intervals	*P* value	Adjusted PR	95% Confidence intervals	*P* value
	Yes		No							
	n 5,371	(%) (75.9)	*n* 1,702	(%) (24.1)						
Peripheral arterial disease										
No	4,714	87.8	1,522	89.4	1.00					
Yes	657	12.2	180	10.6	1.04	1.00-1.08	0.05			
Upper gastrointestinal bleeding										
No	5,249	97,7	1,651	97.0	1.00					
Yes	122	2.3	51	3.0	0.93	0.84-1.02	0.13			
Treatment-related										
Specialty of physician who prescribed ticagrelor										
General practitioner	2,034	37.9	548	32.2	1.00					
Cardiologist	2,771	51.6	986	57.9	0.94	0.91-0.96	<0.01			
Internist	450	8.4	124	7.3	1.00	0.95-1.04	0.84			
Other or missing	116	2.4	44	2.4	0.92	0.83-1.01	0.10			
Number of physician visits										
1st tertile (0-5)	1,828	34.0	414	24.3	1.00			Ref		
2nd tertile (6-10)	1,820	33.9	602	35.4	0.92	0.89-0.95	<0.01	0.90	0.88-0.93	<0.01
3rd tertile (11-224)	1,723	32.1	686	40.3	0.88	0.85-0.91	<0.01	0.86	0.83-0.89	<0.01
Visits to a general practitioner										
No	193	3.6	158	9.3	1.00			Ref		
Yes	5,178	96.4	1,544	90.7	1.40	1.27-1.54	<0.01	1.41	1.29-1.56	<0.01
Visits to a cardiologist										
No	1,378	25.7	354	20.8	1.00					
Yes	3,993	74.3	1,348	79.2	0.94	0.91-0.97	<0.01			
Use of an anticoagulant										
No	5,148	75.8	1,609	94.5	1.00					
Yes	223	4.2	93	5.5	0.93	0.86-0.99	0.04			
Use of clopidogrel or prasugrel										
No	4,513	84.0	1,357	79.7	1.00			Ref		
Yes	858	16.0	345	20.3	0.93	0.89-0.96	<0.01	0.95	0.92-0.99	0.01
Use of statin or fibrate										
No	161	3.0	96	5.6	1.00			Ref		

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Characteristics	Appropriate use				Crude Prevalence Ratio (PR)	95% Confidence intervals	*P* value	Adjusted PR	95% Confidence intervals	*P* value
	Yes		No							
	n 5,371	(%) (75.9)	*n* 1,702	(%) (24.1)						
Yes	5,210	97.0	1,606	94.4	1.22	1.11-1.34	<0.01	1.14	1.04-1.25	0.01
Use of an antihypertensive drug										
No	182	3.4	89	5.2	1.00			Ref		
Yes	5,189	96.6	1,613	94.8	1.14	1.04-1.24	<0.01	1.09	1.00-1.19	0.03
Use of estrogen (in women)										
No	1,690	96.0	545	94.9	1.00					
Yes	71	4.0	29	5.1	0.94	0.83-1.07	0.33			
Use of an antidiabetes drug										
No	4,020	74.8	1,229	72.2	1.00					
Yes	1,351	25.2	473	27.8	0.97	0.94-0.99	0.03			
Use of nitrates										
No	1,581	2.,4	509	29.9	1.00					
Yes	3,790	70.6	1,193	70.1	1.01	0.98-1.03	0.71			
Use of a proton pomp inhibitor										
No	1,886	35.1	628	36.9	1.00					
Yes	3,485	64.9	1,074	63.1	1.02	0.99-1.05	0.18			
Use of a non-steroidal anti-inflammatory drug (other than acetylsalicylic acid)										
No	4,766	88.7	1,487	87.4	1.00					
Yes	605	11.3	215	12.6	0.97	0.93-1.01	0.14			
Total number of different drugs used										
1st tertile (1-9)	1,700	31.7	501	29.4	1.00					
2nd tertile (10-15)	1,986	37.0	644	37.8	0.98	0.95-1.01	0.16			
3rd tertile (16-50)	1,685	31.4	557	32.7	0.97	0.94-1.01	0.10			