



Original Article

Temporal Trends in Fractional Flow Reserve Use in Patients Undergoing Coronary Angiography: A Population-Based Study

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ABSTRACT

Background: Invasive fractional flow reserve (FFR) has emerged as an important tool to identify a subset of patients in whom coronary revascularization may be beneficial. Our objective was to evaluate temporal trends in FFR use.

Methods: We identified all coronary angiograms in the CorHealth Ontario Cardiac Registry between the years 2010 and 2015. The primary and secondary outcomes were the age- and sex-adjusted monthly rate of FFR per 100,000 population and per 100 angiograms, respectively. Piecewise regression analyses were used to evaluate the temporal trends in FFR use for the entire cohort, and then stratified by indication (stable coronary artery disease [CAD]) vs acute coronary syndrome [ACS]).

Results: The study cohort included 379,688 angiograms, of which 122,571 were for stable CAD (32%) and 134,769 were for ACS (36%). Monthly age- and sex-adjusted FFR use rates increased significantly over the study period, from 0.4 to 2.3 per 100,000 people per month. The monthly FFR use rate per 100 angiograms increased from 0.9 to

RÉSUMÉ

Introduction : La réserve de débit fractionnaire (RDF) invasive constitue un outil important pour déterminer un sous-groupe de patients chez qui la revascularisation coronarienne peut être bénéfique. Notre objectif était d'évaluer les tendances temporelles de l'utilisation de la RDF.

Méthodes : Nous avons relevé toutes les angiographies coronariennes dans le registre des soins cardiaques du CorHealth Ontario entre 2010 et 2015. Les critères de jugement principal et secondaire étaient les taux mensuels ajustés à l'âge et au sexe de la RDF par 100 000 personnes et par 100 angiographies, et ce, respectivement. Nous avons utilisé les analyses séquentielles de la régression pour évaluer les tendances temporelles de l'utilisation de la RDF dans la cohorte entière, et nous avons ensuite stratifié par indication (maladie coronarienne [MC] stable) vs syndrome coronarien aigu [SCA]).

Résultats : Dans la cohorte à l'étude, nous avons relevé 379 688 angiographies, dont 122 571 concernaient des MC stables (32 %) et 134 769 concernaient des SCA (36 %). Les taux d'utilisation mensuelle de la RDF ajustée à l'âge et au sexe augmentaient significativement

The foundation of therapy for stable coronary artery disease (CAD) is optimal medical therapy, with or without revascularization, by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Multiple studies have questioned the incremental benefit of PCI over optimal medical therapy.^{1,2} Invasive fractional flow reserve (FFR) has

emerged as an important diagnostic tool to identify a subset of patients in whom revascularization may be beneficial.

There is a growing body of literature that has demonstrated both clinical and economic benefits associated with the use of FFR measurements to guide PCI in patients with stable CAD, with reductions in death, nonfatal myocardial infarction, and urgent revascularization.³⁻⁵ The studies on the utility of FFR in the population with acute coronary syndrome (ACS) are smaller and inconsistent in their conclusions,^{6,7} with some suggesting that the microvascular dysfunction associated with patients with ACS may lead to false-negative FFR results,^{7,8} whereas others maintain FFR are nonetheless valid in this setting.⁹⁻¹² Despite the growing evidence base for FFR in patients with stable CAD and ACS, there is a paucity of data on its use in clinical practice. Specifically, no studies to date have investigated whether the landmark publications on FFR

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Ethics Statement: This study was approved by the Institutional Research Ethics Board at Sunnybrook Health Sciences Centre at the University of Toronto, Ontario.

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See page 17 for disclosure information.

4.9 per 100 angiograms per month; however, the proportion of positive FFR (< 0.8) results was relatively constant at 28%. There was a more dramatic increase in the use of FFR in the population with stable CAD (1.1 to 8.0 per 100 angiograms/month) compared with the population with ACS (0.6 to 4.5 per 100 angiograms/month).

Conclusions: There was a > 5 -fold increase in the use of FFR in patients across Ontario, which was predominantly driven by use in stable CAD. Case selection for FFR use was relatively unchanged with approximately one-quarter of FFR cases being positive over time.

have influenced physician behaviour and affected clinical practice in terms of downstream revascularization decisions.

Accordingly, to address these gaps in knowledge, our aim was to determine the temporal trends in the population rates of FFR overall and for subsets of patients with stable CAD and ACS. We hypothesized that FFR rates would have increased substantially over time with a concomitant decrease in referrals for coronary revascularization.

Material and Methods

This study was approved by the Institutional Research Ethics Board at Sunnybrook Health Sciences Centre at the University of Toronto, Ontario.

Context

Ontario is the largest province in Canada with a population of 13.6 million. All residents have universal access to health care and hospital services through a publicly funded health care program administered by a single third-party payer, the Ontario Ministry of Health and Long Term Care (MOHLTC).

Data sources

Our study used data collected in the CorHealth Ontario Cardiac Registry. The CorHealth Registry captures data from all 19 hospitals that provide invasive cardiac procedures across the province, including cardiac catheterization, PCI, and CABG.^{13,14} The CorHealth Cardiac Registry contains demographic, comorbidity, procedural, and anatomic variables, which have been validated through selected chart abstractions and core laboratory analyses.¹⁵⁻¹⁷ The registry contains a data field specifying the indication for the angiogram as stable CAD or ACS. This registry contains data on the use of FFR, as well as the number of stents used in PCI. Anatomic data were categorized as 1-, 2-, or 3-vessel disease based on the number of epicardial vessels with obstructive disease. We defined obstructive CAD as $> 70\%$ obstruction in any of the left anterior descending artery, circumflex artery, or right coronary artery, or $> 50\%$ obstruction in the left main artery based on visual assessment by the operator of the angiogram.¹⁸ Patients were classified on the basis of the initial revascularization treatment strategy, which was defined as PCI or CABG within 90 days of the index procedure. The 90-day

au cours de la période étudiée, soit de 0,4 à 2,3 par 100 000 personnes par mois. Le taux d'utilisation mensuelle de la RDF par 100 angiographies passait de 0,9 à 4,9 par 100 angiographies par mois. Toutefois, la proportion de résultats positifs de la RDF ($< 0,8$) était relativement stable à 28 %. On observait une augmentation plus considérable dans l'utilisation de la RDF dans la population ayant une MC stable (de 1,1 à 8,0 par 100 angiographies/mois) comparativement à la population ayant un SCA (de 0,6 à 4,5 par 100 angiographies/mois).

Conclusions : On notait une augmentation de l'utilisation de la RDF > 5 fois chez les patients de l'ensemble de l'Ontario. Cette augmentation découlait principalement de l'utilisation lors de MC stable. La sélection de cas pour l'utilisation de la RDF restait relativement inchangée, c'est-à-dire qu'environ un quart des cas de RDF obtenait des résultats positifs avec le temps.

window was chosen on the basis of previous literature and current wait times in Ontario.^{15,16,19,20}

Data from the CorHealth Cardiac Registry were linked using encrypted unique patient identifiers to population-based administrative databases housed at the Institute for Clinical Evaluative Sciences in Toronto, Ontario. Validated Institute for Clinical Evaluative Sciences—derived databases were used to identify diabetes (Ontario Diabetes Dataset),²¹ congestive heart failure (Ontario Congestive Heart Failure Dataset),²² and hypertension (Ontario Hypertension Dataset).²³ Linkages were performed to the Canadian Institute for Health Information Discharge Abstract Database and the Ontario Health Insurance Plan physician claims database to confirm several cardiac status and risk factors using a look-back period of 3 to 20 years before the index coronary angiogram. Linkages to these population-level administrative databases were also used to identify interventional and surgical cardiac procedures occurring after the index coronary angiogram. The Institution Information System, which contains information about Ontario health care institutions funding by the MOHLTC, was used to classify hospitals as academic or community. Demographic information (age and gender) was determined through linkage with vital statistics in the Registered Persons Database.

Patient selection

We included all the patients captured in the CorHealth database who underwent a coronary angiography in Ontario for CAD from January 1, 2010, to December 31, 2015. In our study, the unit of analysis was the angiogram.

The total cohort was divided into 3 subcohorts: (1) stable CAD subcohort, which included patients referred for angiography for the indication of stable CAD with a Canadian Cardiovascular Society functional angina classification of 0 to 4 and who were waiting for their coronary angiogram at home; (2) ACS subcohort, which included patients referred for angiography for unstable angina (UA), non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction, with a classification of ACS as emergent, high risk, intermediate, or low risk; and (3) an indeterminate subcohort, which included patients who are not clearly in either of these 2 subcohorts. We choose this classification to ensure high specificity with patients in the stable CAD and ACS groups, because this was the main comparison of interest.

On the basis of the CorHealth registry, we ascertained if each angiogram was associated with an FFR. An additional subanalysis was conducted to assess clinical outcomes stratified by FFR result (positive < 0.8 vs negative > 0.8); this analysis was restricted to angiograms after April 5, 2013, because these data were only captured in the CorHealth registry from this date onward.

Outcome variable

Our primary outcome of interest was the monthly age- and sex-standardized population rate of FFR per 100,000 (direct standardization using the 2010 Ontario population). As a metric of FFR use per case, our secondary outcome was the monthly rate of FFR per 100 angiograms in the whole cohort and then in each of the stable CAD and ACS subcohorts. Finally, as a metric of FFR case selection over time, we also examined the proportion of positive FFR results per month over the study period.

Our clinical outcome of interest was to evaluate the proportion of patients who had a subsequent PCI and CABG within 3 months of the index angiogram. This time period was based on the upper limits of procedural wait-times in the province over that study period.²⁴ We also evaluated the number of stents that were used for each subsequent PCI.

Statistical analysis

For the trend analysis of FFR use rates over time, piecewise regression analyses were performed. The dependent variable was the age- and sex-standardized FFR use rate per 100,000 of the population or the rate of FFR use per 100 angiograms. We evaluated the impact on FFR use rates in response to the landmark study “Fractional Flow Reserve Guided PCI versus Medical Therapy in Stable Coronary Disease” (FAME 2 trial), which was published in September 2012.⁴ Residuals were plotted over time, and the Durbin–Watson statistic was used to determine whether first-order autocorrelation was present. If autocorrelation was present, the autoregressive parameters were included in the final piecewise regression model for correction. A simple z score test was used to determine the significance of the difference between the piecewise regression slopes. We repeated these analyses in subgroups of patients treated at academic centers vs community hospitals. All data analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 379,688 coronary angiograms were performed between January 1, 2010, and December 31, 2015. As shown

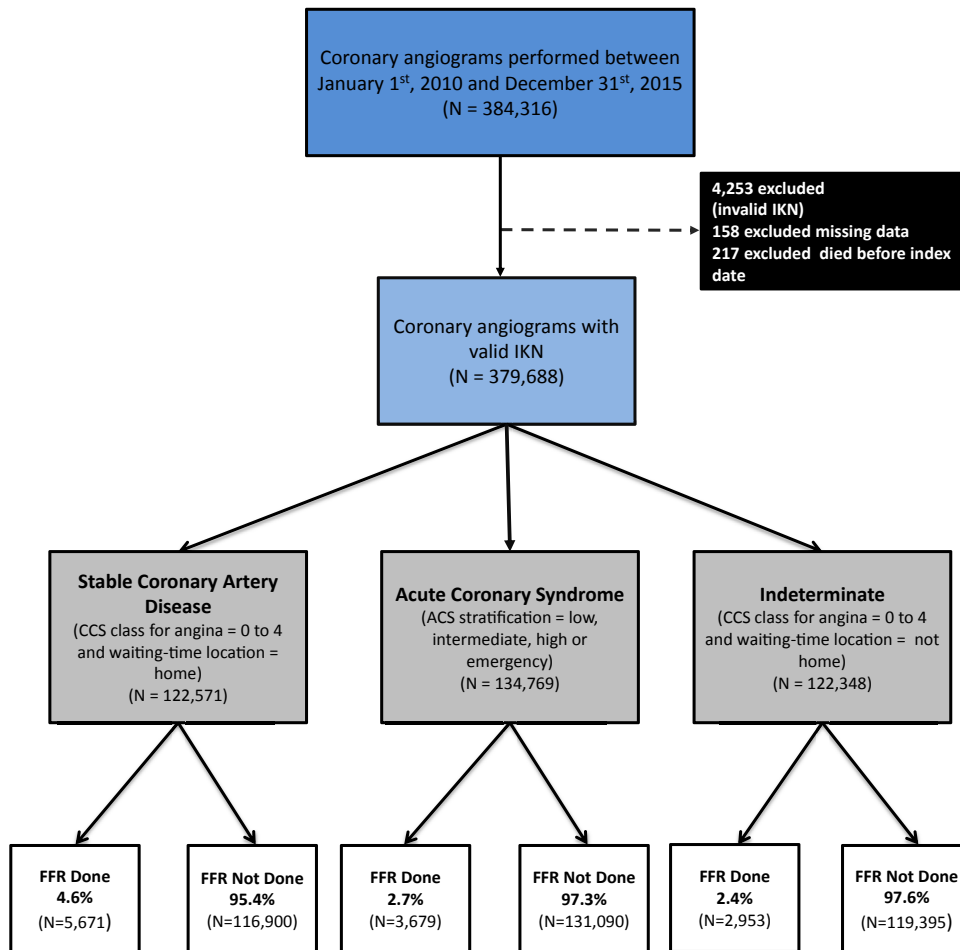


Figure 1. Selection of patient’s cohort. ACS, acute coronary syndrome; CCS, Canadian Cardiovascular Society; FFR, fraction flow reserve; IKN, unique identifier.

Table 1. Baseline characteristics in patients who underwent coronary angiography in Ontario between January 1, 2010, and December 31, 2015 (N = 379,688)

Variable	Total N = 379,688	FFR N = 12,303	Non-FFR N = 367,385	Standardized difference	P value
Demographics					
Age Mean ± SD, y	64.97 ± 12.12	65.13 ± 10.67	64.97 ± 12.16	0.04	0.15
Sex, female, N (%)	131,899 (34.7%)	4015 (32.6%)	127,884 (34.8%)	0.05	< 0.001
Clinical presentation, N (%)					
Elective stable CAD	131,300 (34.6%)	5432 (44.2%)	125,868 (34.3%)	0.20	< 0.001
Rule out CAD	29,672 (7.8%)	875 (7.1%)	28,797 (7.8%)	0.03	
STEMI	43,893 (11.6%)	466 (3.8%)	43,427 (11.8%)	0.30	
NSTEMI	74,591 (19.6%)	1964 (16.0%)	72,627 (19.8%)	0.10	
UA	67,891 (17.9%)	3200 (26%)	64,691 (17.6%)	0.25	
Unknown	32,341 (8.5%)	366 (3.0%)	31,975 (8.7%)	0.25	
Medical comorbidities, N (%)					
Previous MI	140,548 (37%)	5089 (41.4%)	135,459 (36.9%)	0.09	< 0.001
CVD	29,599 (7.8%)	902 (7.3%)	28,697 (7.8%)	0.02	0.05
Previous CABG	44,392 (11.7%)	1006 (8.2%)	43,386 (11.8%)	0.12	< 0.001
Previous PCI	107,786 (28.4%)	5703 (46.4%)	102,083 (27.8%)	0.39	< 0.001
DM	123,316 (32.5%)	4347 (35.3%)	118,969 (32.4%)	0.06	< 0.001
HTN	265,543 (69.9%)	9368 (76.1%)	256,175 (69.7%)	0.15	< 0.001
HLD	249,569 (65.7%)	9175 (74.6%)	240,394 (65.4%)	0.20	< 0.001
Current smoking	78,359 (20.6%)	2368 (19.2%)	75,991 (20.7%)	0.04	0.001
PVD	26,115 (6.9%)	865 (7.0%)	25,250 (6.9%)	0.06	0.50
CHF	53,867 (14.2%)	1280 (10.4%)	52,587 (14.3%)	0.12	< 0.001
Renal disease	14,620 (3.9%)	351 (2.9%)	14,269 (3.9%)	0.06	< 0.001
LVEF%, N (%)					
4: < 20%	5129 (1.4%)	73 (0.6%)	5056 (1.4%)	0.08	< 0.001
3: 20%-34%	17,316 (4.6%)	405 (3.3%)	16,911 (4.6%)	0.07	
2: 35%-49%	34,088 (9%)	1137 (9.2%)	32,951 (9.0%)	0.01	
1: > 50%	138,144 (36.4%)	5510 (44.8%)	132,634 (36.1%)	0.18	
Unknown	185,011 (48.7%)	5178 (42.1%)	179,833 (48.9%)	0.14	
Angiographic findings, No. of diseased vessels, N (%)					
0	144,158 (38%)	4313 (35.1%)	139,845 (38.1%)	0.07	< 0.001
1	103,121 (27.2%)	4141 (33.7%)	98,980 (26.9%)	0.15	
2	71,658 (18.9%)	2673 (21.7%)	68,985 (18.8%)	0.07	
3	60,751 (16%)	1176 (9.6%)	59,575 (16.2%)	0.20	
Mean ± SD (N)	1.13 ± 1.09 (379,688)	1.06 ± 0.97 (12,303)	1.13 ± 1.1 (367,385)	0.07	< 0.001
Hospital type					
Academic	207,476 (54.6%)	7306 (59.4%)	200,170 (54.5%)	0.10	< 0.001
Community	172,212 (45.4%)	4997 (40.6%)	167,215 (45.5%)	0.10	

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; DM, diabetes mellitus; FFR, fractional flow reserve; HLD, hyperlipidemia; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N, refers to patient's number; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

in Figure 1, there were 122,571 angiograms performed for stable CAD and 134,769 angiograms performed for ACS. FFR was performed in 3.2% of the total cohort and in 4.6%, 2.7%, and 2.4% in the stable CAD, ACS, and indeterminate subcohorts, respectively.

Baseline characteristics

The baseline characteristics of the whole cohort and individually in the 3 subcohorts, stratified by FFR status (FFR vs non-FFR), are shown in Table 1 and Supplementary Tables S1-S3. In general, FFR was used more commonly in stable CAD cases with greater symptom burden, as quantified by the Canadian Cardiovascular Society class (Supplementary Table S1). The converse was true in ACS cases, in which FFR was more frequently used in those with lower-risk presentations (Supplementary Table S2). The baseline characteristics for the subgroup in which FFR results are reported, starting in April 5, 2013, are presented in Supplementary Tables S4 and S5. In this subgroup of 178,792 angiograms, FFR was conducted in 7775 cases (4.3%). Overall, this subgroup was similar in terms of baseline characteristics to the overall cohort.

Trends in FFR use

As shown in Figure 2, the rate of FFR use (age- and sex-standardized population rate of FFR per 100,000) in Ontario increased substantially during the study period from approximately from 0.4 to 2.3 per 100,000 people per month. This increase in FFR use reflected an increased use per angiogram, as shown in Figure 3A-C. The monthly FFR use rate increased from 0.9 to 4.9 per 100 angiograms/month in the overall cohort (Fig. 3A). The rate of FFR use during the study period increased 1.5 times faster in the stable CAD (1.1 to 8.0 per 100 angiograms/month) (Fig. 3B) compared with the ACS population (0.6 to 4.5 per 100 angiograms/month) (Fig. 3C). However, this difference did not reach statistical significance (z score 0.14). As a reflection of case selection, despite the increase in overall rates of FFR per population and by angiogram, the proportion of FFR cases that were positive did not change significantly during the study period, remaining at approximately 28% (Fig. 4).

As shown in Figures 2 and 3A-C, there were minimal differences in the rates of FFR use after the publication of FAME-2 in September 2012 (Supplementary Table S6 shows details).

Trends in FFR use in academic vs community hospitals

As shown in [Supplementary Figure S1](#), the rate of FFR use (age- and sex-standardized population rate of FFR per 100,000 people/month) increased during the study period in academic and community hospitals from approximately 0.3 to 1.3 and from 0.1 to 1.1, respectively. The relative increase in FFR use per 100 angiograms per month was greater in community vs academic hospitals (0.5 to 5.2 and 1.6 to 4.6, respectively) ([Supplementary Fig. S1](#)). The proportion of FFR cases that were positive did not change significantly during the study period, remaining at approximately 30% in academic hospitals and 26% in community hospitals ([Supplementary Fig. S2](#)). As with our main findings, the publication of FAME-2 was associated with minimal differences in FFR use in both the academic and the community hospitals overall, as well as in the stable CAD and ACS populations ([Supplementary Figures S1 and S3](#)).

Clinical outcomes

As shown in [Table 2](#), there were inconsistent observations insofar as subsequent revascularization. In the total cohort, a significantly higher proportion of cases in the FFR group were referred for PCI (35.7% vs 33.3%, $P < 0.001$), whereas fewer cases in the FFR group were referred to CABG (10.8% vs 11.8%, $P < 0.001$). This pattern was also seen in the stable CAD subgroup. In contrast, in the ACS group, we observed the opposite pattern, in which fewer cases in the FFR group underwent subsequent PCI (41.2% vs 54.5% $P < 0.001$). Similar trends were observed in the subgroups of community vs academic hospitals ([Supplementary Table S7](#)).

Subgroup analysis

Similar to the overall group, in the subgroup analysis of angiograms after April 5, 2013, we found a higher proportion of cases in the FFR group were referred for PCI (36.3% vs 33.8%, $P < 0.001$) ([Supplementary Table S4](#)). We compared angiograms with positive vs negative FFR results ([Supplementary Table S5](#)). The FFR was positive (<0.8) in 2153 cases (27.7%). As expected, a significantly higher proportion of cases with positive FFR results underwent subsequent revascularization. Of note, 1631 (29%) of the 5622 cases in the negative FFR group underwent PCI. Further characteristics of these patients are shown in [Supplementary Table S8](#).

Discussion

We found a 5-fold increase in the use of FFR in angiograms across Ontario between 2010 and 2015. Case selection for FFR remained almost the same with approximately one-quarter of FFR cases being positive over time. FFR was used more commonly in stable CAD cases with greater symptom burden, as a rule-in procedure. In contrast, in the ACS cases, FFR was more frequently used in those with lower-risk presentations, as a rule-out procedure. Consistent with this pattern, there was higher subsequent PCI referral rates observed in the stable CAD subcohort compared with the ACS subcohort.

Previous studies have shown an increase in the use of FFR since the seminal FAME study, focusing on practice from

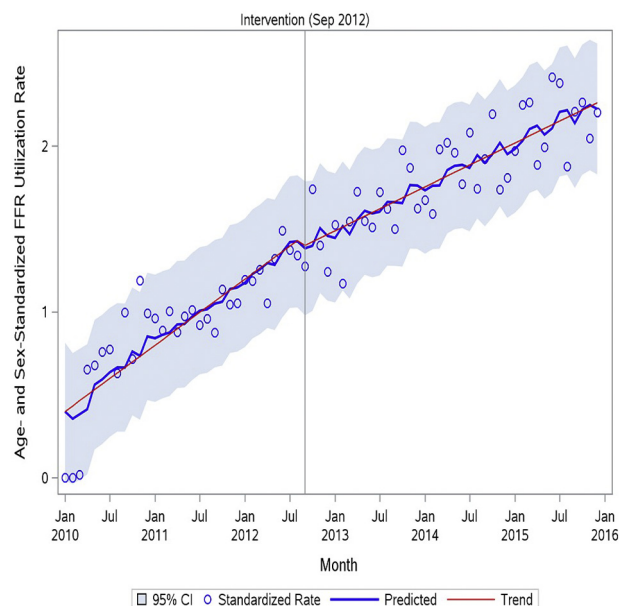


Figure 2. Monthly age- and sex-standardized FFR use rates per 100,000 population in Ontario (January 1, 2010, to December 31, 2015). CI, confidence interval; FFR, fraction flow reserve.

2001 to 2013.²⁵⁻²⁹ Indeed, more than 70% of physicians thought that the FAME trial led to more widespread use of FFR.²⁵ Harle et al.²⁹ found a very low rate of FFR; nonetheless, they observed an increasing trend in use over the course of the study period. The use of FFR was particularly low in patients with multivessel disease. There was wide variation in FFR use across the 38 hospitals participating in the study.²⁹ Our study builds on this previous literature by evaluating FFR use in a more contemporary era. We found an ongoing increase in the use of FFR in patients across Ontario, which was predominantly driven by the use in cases with stable CAD. Although we did find a higher rate of FFR use in multiple-vessel disease at approximately 10% compared with earlier studies ($\sim 2.5\%$), this was lower than 1- or 2-vessel disease.²⁹ We did not find that the publication of FAME-2 was associated with any acceleration in the increase in use, and if anything, an attenuation in the total cohort and even a statistically significant decrease in the ACS subcohort. We would emphasize that these decreases are very small (0.13 FFR per 100,000) and therefore of no clinical significance. We hypothesize that this is because this additional literature reinforced the acceptance of FFR, rather than modified previous clinical attitudes.

Our findings on the FFR use trends in the ACS population were unexpected. Despite the relative paucity of data on its validity, the rate of FFR use in patients with ACS was relatively high at 2.6% and increased throughout the study period. The different symptom burden and risk in the stable CAD and ACS cases merit discussion. The fact that patients with stable CAD undergoing FFR were more symptomatic suggests that this was used as a test to confirm severe disease when anatomic features did not suggest this. In contrast, the lower risk of patients with ACS undergoing FFR suggest the opposite—that FFR was done to rule out a significant lesion.

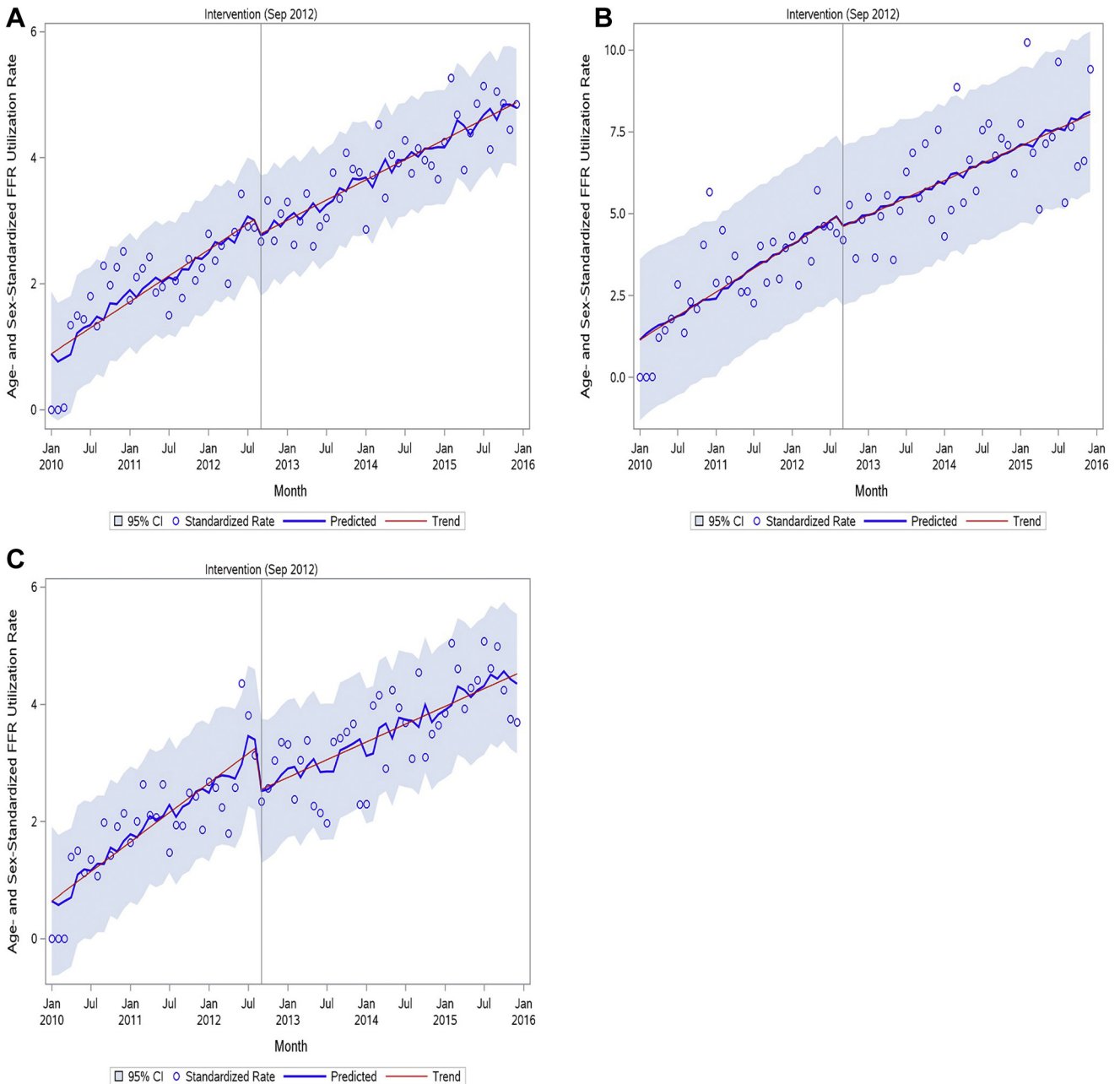


Figure 3. (A) Monthly age- and sex-standardized FFR use rates per 100 angiograms (January 1, 2010, to December 31, 2015). (B) Monthly age- and sex-standardized FFR use rates per 100 angiograms in patients with stable CAD (January 1, 2010, to December 31, 2015). (C) Monthly age- and sex-standardized FFR use rates per 100 angiograms in patients with ACS (January 1, 2010, to December 31, 2015). CI, confidence interval; FFR, fraction flow reserve.

Our hypothesis regarding these opposite intentions is further suggested by the inconsistent observations in subsequent revascularization in the populations. In the stable CAD subcohort, a significantly higher proportion of cases in the FFR group were referred for PCI, in contrast to the ACS cases. This reinforces our inference that FFR was applied as a rule-in tool for stable CAD vs a rule-out tool in patients with ACS. Unfortunately, only a portion of our cohort had information on the results of the FFR, and even in these cases there was a relative lack of granular information. For example, we are not able to confirm if the FFR in ACS cases was performed on a

nonculprit lesion. Moreover, we found that approximately 29% of cases with a negative FFR had subsequent PCI. It is likely that this was PCI in a different coronary artery, and indeed, approximately 40% of those cases were multiple-vessel disease. That said, we lack the necessary granularity in the registry to fully understand this observation, but it merits further study. If indeed PCI was performed in FFR-negative cases, it may suggest that some physicians do not have as much confidence in FFR results in comparison with their visual assessment of the angiogram, a finding that if true should be a target for both education and quality improvement efforts.

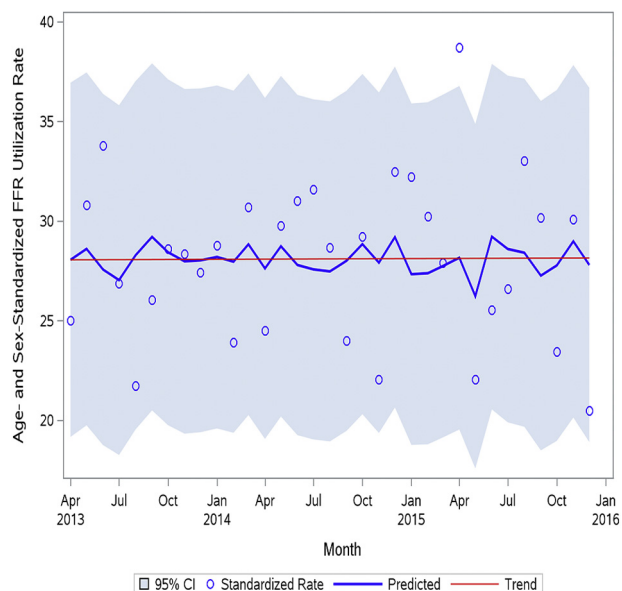


Figure 4. Proportion of positive FFR results (April 5, 2013, to December 31, 2015). CI, confidence interval; FFR, fraction flow reserve.

Study limitations

Our study must be interpreted in the context of several additional limitations that merit discussion. Given the availability of FFR data in the CorHealth registry; the study cohort could only contain angiograms performed after 2010; as such, we cannot comment on practice change that corresponded to the initial FAME publications. Second, our data showed that FFR use resulted in higher rates of PCI referrals in the total cohort and in the stable CAD subcohort; however, we are unable to comment whether this translated to improved outcomes. This is an area of ongoing research by our group. Third, our indeterminate subcohort was relatively large. We elected to be conservative in our classification of stable CAD vs ACS because this was the main comparison of interest. This results in a high specificity for cases allocated to the stable CAD or ACS groups, but correspondingly, a large proportion classified as indeterminate. Because we only included patients in our cohort with a referral for the investigation of coronary disease, it is likely that most of indeterminate patients were, in fact, either patients with stable CAD or patients with ACS; on the basis of the information in the registry, we were simply not able to classify them accurately. Indeed, the observation that the indeterminate subcohort showed the same upward

Table 2. Clinical outcomes in patients who underwent coronary angiogram in Ontario between January 1, 2010, and December 31, 2015

Total cohort	Total, N = 379,688	FFR, N = 12,303	Non-FFR, N = 367,385	Standardized difference	P value
Clinical outcomes, N (%)					
PCI within 3 mo	126,572 (33.3%)	4395 (35.7%)	122,177 (33.3%)	0.05	< 0.001
CABG within 3 mo	44,794 (11.8%)	1331 (10.8%)	43,463 (11.8%)	0.03	0.001
No. of stents in PCI, N (%)					
1	74,238 (58.7%)	2629 (59.8%)	71,609 (58.6%)	0.03	0.28
2	34,160 (27%)	1150 (26.2%)	33,010 (27.0%)	0.02	
3+	18,174 (14.4%)	616 (14.0%)	17,558 (14.4%)	0.01	
Stent No. Mean ± SD	1.62 ± 0.92 (126,572)	1.6 ± 0.91 (4395)	1.62 ± 0.92 (122,177)	0.02	0.15
Stable CAD subgroup					
Total, N = 122,571		FFR, N = 5671	Non-FFR, N = 116,900	Standardized difference	P value
Clinical outcomes, N (%)					
PCI within 3 mo	32,679 (26.7%)	1847 (32.6%)	30,832 (26.4%)	0.13	< 0.001
CABG within 3 mo	16,683 (13.6%)	527 (9.3%)	16,156 (13.8%)	0.14	< 0.001
No. of stents in PCI, N (%)					
1	18,316 (56%)	1110 (60.1%)	17,206 (55.8%)	0.09	0.001
2	8973 (27.5%)	467 (25.3%)	8506 (27.6%)	0.05	
3+	5390 (16.5%)	270 (14.6%)	5120 (16.6%)	0.05	
Stent no. mean ± SD	1.68 ± 0.97 (32,679)	1.61 ± 0.91 (1847)	1.69 ± 0.97 (30,832)	0.08	0.001
ACS subgroup					
Total, N = 134,769		FFR, N = 3679	Non-FFR, N = 131,090	Standardized difference	P value
Clinical outcomes, N (%)					
PCI within 3 mo	72,918 (54.1%)	1515 (41.2%)	71,403 (54.5%)	0.27	< 0.001
CABG within 3 mo	17,067 (12.7%)	479 (13.0%)	16,588 (12.7%)	0.01	0.51
No. of stents in PCI, N (%)					
1	43,845 (60.1%)	889 (58.7%)	42,956 (60.2%)	0.03	0.50
2	19,488 (26.7%)	422 (27.9%)	19,066 (26.7%)	0.03	
3+	9585 (13.1%)	204 (13.5%)	9381 (13.1%)	0.01	
Stent no. mean ± SD	1.59 ± 0.89 (72,918)	1.61 ± 0.89 (1515)	1.59 ± 0.89 (71,403)	0.02	0.44
Indeterminate subgroup					
Total, N = 122,348		FFR, N = 2953	Non-FFR, N = 119,395	Standardized difference	P value
Clinical outcomes, N (%)					
PCI within 3 mo	20,975 (17.1%)	1033 (35.0%)	19,942 (16.7%)	0.43	< 0.001
CABG within 3 mo	11,044 (9%)	325 (11.0%)	10,719 (9.0%)	0.07	< 0.001
No. of stents in PCI, N (%)					
1	12,077 (57.6%)	630 (61.0%)	11,447 (57.4%)	0.07	0.07
2	5699 (27.2%)	261 (25.3%)	5438 (27.3%)	0.05	
3+	3199 (15.3%)	142 (13.7%)	3057 (15.3%)	0.05	
Stent no. mean ± SD	1.65 ± 0.95 (20,975)	1.59 ± 0.92 (1033)	1.65 ± 0.96 (19,942)	0.07	0.03

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; N, refers to patient's number; PCI, percutaneous coronary intervention; SD, standard deviation.

trend in FFR use as the others reinforces this point. Finally, our observations were at an ecologic level, and as such, we do not imply any causality. Therefore, it is important that our inferences be considered hypothesis generating and not conclusive.

Conclusions

There is a strong temporal trend of increasing FFR use overall and in both subsets of patients with stable CAD and ACS. We found that case selection, as reflected by the proportion of positive FFR results, has remained relatively constant over time.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-16.
2. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31-40.
3. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
4. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
5. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010;56:177-84.
6. Shah NR, Al-Lamee R, Davies J. Fractional flow reserve in acute coronary syndromes: a review. *Int J Cardiol Heart Vasc* 2014;5:20-5.
7. Sulimov DS, Abdel-Wahab M, Richardt G. Fractional flow reserve in acute myocardial infarction: a guide for non-culprit lesions? *Cardiol Ther* 2015;4:39-46.
8. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol* 2012;59:1045-57.
9. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386:665-71.
10. Hofsten DE, Kelbaek H, Helqvist S, et al. The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: ischemic postconditioning or deferred stent implantation versus conventional primary angioplasty and complete revascularization versus treatment of culprit lesion only: rationale and design of the DANAMI 3 trial program. *Am Heart J* 2015;169:613-21.
11. Ntalianis A, Sels JW, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010;3:1274-81.
12. Layland J, Carrick D, McEntegart M, et al. Vasodilatory capacity of the coronary microcirculation is preserved in selected patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2013;6:231-6.
13. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI II A results. The TIMI Research Group. *JAMA* 1988;260:2849-58.
14. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50:e1-157.
15. Bennell MC, Qiu F, Kingsbury KJ, Austin PC, Wijeyesundera HC. Determinants of variations in initial treatment strategies for stable ischemic heart disease. *CMAJ* 2015;187:E317-25.
16. Tu JV, Ko DT, Guo H, et al. Determinants of variations in coronary revascularization practices. *CMAJ* 2012;184:179-86.
17. Ko DT, Tu JV, Austin PC, et al. Prevalence and extent of obstructive coronary artery disease among patients undergoing elective coronary catheterization in New York State and Ontario. *JAMA* 2013;310:163-9.
18. Bradley SM, Maddox TM, Stanislawski MA, et al. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insights from the VA CART program (veterans affairs clinical assessment reporting and tracking). *J Am Coll Cardiol* 2014;63:417-26.
19. Min JK, Berman DS, Dunning A, et al. All-cause mortality benefit of coronary revascularization vs medical therapy in patients without known coronary artery disease undergoing coronary computed tomographic angiography: results from CONFIRM (CORonary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). *Eur Heart J* 2012;33:3088-97.
20. CCN Ontario Annual Report 2015-16. Available at: <https://www.corhealthontario.ca/CCN-Annual-Report-2015-16.pdf>. Accessed January 10, 2019.
21. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512-6.

22. Schultz SE, Rothwell DM, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can* 2013;33:160-6.
23. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Med* 2007;1:e18-26.
24. Wait-time Alliance. Available at: <http://www.waittimealliance.ca/about-us/>. Accessed January 31, 2018.
25. Hannawi B, Lam WW, Wang S, Younis GA. Current use of fractional flow reserve: a nationwide survey. *Tex Heart Inst J* 2014;41:579-84.
26. Riley RF, Don CW, Powell W, Maynard C, Dean LS. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circ Cardiovasc Qual Outcomes* 2011;4:193-7.
27. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. *J Am Coll Cardiol* 2012;60:2337-9.
28. Pothineni NV, Shah NN, Rochlani Y, et al. U.S. trends in inpatient utilization of fractional flow reserve and percutaneous coronary intervention. *J Am Coll Cardiol* 2016;67:732-3.
29. Harle T, Zeymer U, Hochadel M, et al. Real-world use of fractional flow reserve in Germany: results of the prospective ALKK coronary angiography and PCI registry. *Clin Res Cardiol* 2017;106:140-50.

Supplementary Material

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