Effect of operator and institutional volume on clinical outcomes after percutaneous coronary interventions performed in Canada and the United States: A brief report from the Enhanced Suppression of the Platelet glycoprotein IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) study

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BACKGROUND: The Enhanced Suppression of the Platelet glycoprotein IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial compared the use of eptifibatide with placebo in 2064 coronary intervention patients. It was previously reported that Canadian patients had reduced rates of 30-day and one-year death, myocardial infarction (MI) or target-vessel revascularization (TVR) compared with patients in the United States (US).

OBJECTIVE: To examine whether operator or institutional volume differences explain the regional variation in clinical outcome.

METHODS AND RESULTS: Each site received an operator and institutional volume survey. Fifty-seven sites (62%) returned complete data on 1338 patients. In this smaller cohort, Canadian patients had reduced rates of 30-day and one-year death, MI or TVR compared with US patients (6.3% versus 10.3% and 14.9% versus 20.1%, respectively; $P < 0.05$ for both comparisons). Among 176 physicians with a median of 13 years experience, the median operator volume was 200 cases per year. Operators with fewer than 100 cases per year had higher rates of 30-day death, MI or TVR (13.2% versus 8.7%; $P = 0.18$) and large MI (7.7% versus 3.3%; $P = 0.06$) than those with 100 or more cases per year. The median institutional volume was 1064 cases per year. Canadian and US centres had similar operator and institutional volumes. By multivariate modelling, operator volume was not predictive of adverse clinical events. However, the rates of 30-day and one-year death, MI or TVR fell by 3% for every 100 patients treated by the institution (OR 0.97; $P = 0.058$ and $P = 0.002$, respectively). Enrollment in Canada was associated with improved outcomes at 30 days (OR 0.50; $P = 0.001$) and one year (OR 0.66; $P = 0.001$) despite inclusion of volume variables in the models.

CONCLUSIONS: In the ESPRIT study, institutional volume was associated with a modest reduction in risk of death, MI or TVR over short- and long-term follow-up periods. The Canadian and US investigators and institutions selected in ESPRIT had similar annual procedural volumes. Therefore, volume variables did not explain the differential risk of clinical events observed for patients enrolled in the two countries.

Key Words: Canada; Operator volume; United States

L'effet du volume de l'opérateur et de l'établissement sur les issues cliniques après des interventions coronaires percutanées effectuées au Canada et aux États-Unis : Un bref rapport de l'étude ESPRIT sur la suppression améliorée du récepteur plaquettaire des glycoprotéines IIb/IIIa au moyen d'une thérapie à l'intégriline

HISTORIQUE : L'étude ESPRIT sur la suppression améliorée du récepteur plaquettaire des glycoprotéines IIb/IIIa au moyen d'une thérapie à l'intégriline comparait l'utilisation d'éptifibatide à celle d'un placebo chez 2 064 patients subissant une intervention percutanée. Il avait déjà été établi que les patients du Canada avaient des taux réduits de décès au bout de 30 jours et d'un an, d'infarctus du myocarde (IM) ou de revascularisation de vaisseaux ciblés (RVC) par rapport aux patients des États-Unis.

OBJECTIF : Examiner si les différences entre le volume de l'opérateur ou de l'établissement expliquent la variation régionale en matière d'issues cliniques.

MÉTHODOLOGIE ET RÉSULTATS : Chaque établissement a reçu un sondage sur le volume de l'opérateur et de l'établissement. Cinquante-sept établissements (62 %) ont retourné des données complètes sur 1 338 patients. Dans cette cohorte plus petite, les patients canadiens présentaient un taux réduit de décès au bout de 30 jours et d'un an, d'IM ou de RVC par rapport aux patients des États-Unis (6,3 % par rapport à 10,3 % et 14,9 % par rapport à 20,1 %, respectivement; $P < 0,05$ dans les deux comparaisons). Chez les 176 médecins ayant une expérience médiane de 13 ans, le volume médian de l'opérateur était de 200 cas par année. Les opérateurs voyant moins de 100 cas par année présentaient un taux plus élevé de décès au bout de 30 jours, d'IM ou de RVC (13,2 % par rapport à 8,7 %; $P = 0,18$) et de gros IM (7,7 % par rapport à 3,3 %; $P = 0,06$) que ceux en voyant au moins 100 par année. Le volume médian de l'établissement était de 1 064 cas par année. Les centres canadiens et américains présentaient un volume similaire de l'opérateur et de l'établissement. D'après le modelage multivarié, le volume de l'opérateur n'était pas prédictif des événements cliniques négatifs. Cependant, les taux de décès au bout de 30 jours et d'un an, d'IM et de RVC diminuaient de 3 % par tranche de 100 patients traités par l'établissement (RRR 0,97; $P = 0,058$ et $P = 0,002$, respectivement). La participation au Canada s'associait à une meilleure issue au bout de 30 jours (RRR 0,50; $P = 0,001$) et d'un an (RRR 0,66; $P = 0,01$) malgré l'inclusion des variables de volume dans le modèle.

CONCLUSIONS : Dans l'étude ESPRIT, le volume de l'établissement s'associait à une modeste réduction du risque de décès, d'IM ou de RVC pendant des périodes de suivi à court et à long terme. Les médecins et les établissements canadiens et américains sélectionnés pour l'étude ESPRIT présentaient un volume annuel similaire d'interventions. Ainsi, les variables de volume n'expliquaient pas le risque différentiel d'événements cliniques observé chez les patients des deux pays.

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An inverse relationship between the annual number of patients treated by a hospital or physician and rates of ischemic complications after percutaneous coronary intervention (PCI) has been well established by previous publications (1-6). Although the interpretation of this literature with regard to policy making is controversial, such data have been used to establish the current American College of Cardiology recommendations for a minimum operator volume of 75 cases per year and a minimum institutional volume of 200 procedures per year (ideally 400 or more PCIs per year) to maintain both operator and institutional competence (7).

The Enhanced Suppression of the Platelet glycoprotein IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial (8) compared the use of eptifibatide with placebo in 2064 patients undergoing PCI. We previously demonstrated that Canadian patients enrolled in ESPRIT had reduced rates of 30-day and one-year death, myocardial infarction (MI) or target vessel revascularization (TVR) compared with patients in the United States (US) (9). This association persisted after extensively adjusting for multiple baseline differences between Canadian and US patients. The current study was performed to examine the effect of operator and institutional volume on clinical outcomes in ESPRIT and whether these variables explained the previously reported regional variation in outcome. Our main hypothesis was that the lower adverse event rate observed among Canadians could be explained by higher operator and institutional PCI volumes at Canadian centres than at US centres.

METHODS

ESPRIT study

The design and methods of the ESPRIT trial, and the Canada versus US analysis were reported previously (8,9). Briefly, 92 investigational sites (11 Canadian centres and 81 US centres) enrolled 2064 patients. Patients were eligible for participation in ESPRIT if they were scheduled to undergo nonurgent stenting of a native coronary artery without planned use of glycoprotein IIb/IIIa inhibition. The main exclusion criteria consisted of patients with an MI within 24 h or chest pain precipitating urgent PCI, or treatment with a thienopyridine more than 24 h before random assignment. PCI was performed according to local standards. Patients were randomly assigned to receive either placebo or double-bolus eptifibatide immediately before PCI. All patients received acetylsalicylic acid and weight-adjusted heparin. It was recommended that thienopyridine therapy be initiated no more than 24 h before PCI. The choice of thienopyridine, the timing of therapy and the use of a loading dose were according to local practice.

Definitions

In the Canada and US analysis of the ESPRIT trial, clinical outcomes were reported according to country of enrollment. The key end points for this analysis were the combined incidence of death, MI or TVR at 30 days and one year. TVR was defined as a subsequent revascularization procedure performed on the original target vessel. At 30 days, urgent TVR was assessed. At one year, the incidence of any TVR was studied. Either enzymatic or clinical criteria defined an end point MI. An 'enzymatic' MI occurred when at least two measures of creatine kinase-myocardial band isoenzyme assessed by the central core laboratory were elevated to at least three times the upper limit of normal within 24 h of PCI. For a period of 24 h after PCI, creatine kinase-myocardial band was assessed every 6 h. After the first 24 h, a 'clinical' MI could be reported by an investigator and adjudicated by a clinical events committee. A 'clinical' MI report required confirmation by the presence of clinical symptoms and supportive electrocardiographic or cardiac marker data. In cases of repeat PCI or bypass surgery, cardiac marker elevations to at least three or five times the upper limit of normal were required.

Operator volume survey

The survey was conducted from June 2002 to December 2003. A questionnaire was mailed to all sites requesting information regarding

academic status, and operator and institutional volume during 1999 and 2000 (period of ESPRIT trial enrollment). At each centre, each operator performing PCI on an ESPRIT patient was assigned a unique numerical identifier (ie, operator 100-001, 100-002, etc). Each ESPRIT operator completed the survey anonymously. The sites were asked to confidentially report which operator performed PCI for each unique study number/patient enrolled in ESPRIT using the operator identification numbers so that the survey investigators were blinded to the identity of the operators at each site. After the initial mailing, nonresponding sites were followed up with a fax request and two subsequent telephone requests to return the survey.

Statistical analysis

Intention-to-treat analyses related to the use of eptifibatide or placebo were performed. Categorical variables are presented as counts and percentages, while continuous measures are presented as medians with interquartile ranges as measures of variability. Groupwise comparisons were performed using χ^2 analyses for categorical variables and Wilcoxon's rank sum tests for continuous variables. Unadjusted comparisons of Canadian and US patients were made using likelihood ratio χ^2 tests for 30-day end points and log-rank tests for one-year analyses. Kaplan-Meier survival curves were generated by plotting the time to first occurrence for any component of the one-year composite end point. Multivariate logistic regression was used to assess the relationship of operator volume and institutional volume with the 30-day and one-year composite end points of death, MI or TVR. To account for any possible confounding between volume measures and other end point predictors, these models also included predictors previously identified for the full ESPRIT cohort (8). Each model included generalized estimating equations to account for the correlation among patients treated by the same physician or at the same institution. Average volumes during 1999 and 2000 were used for data analysis. Clinical outcomes were evaluated among low- and high-volume operators (fewer than 100 cases per year, or 100 cases or more per year) using likelihood ratio χ^2 tests for 30-day end points and log-rank tests for one-year analyses. Two-sided probability values are reported, with $P < 0.05$ considered to be statistically significant. Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, USA).

RESULTS

Completed surveys were received from 57 sites (62%), representing 1338 of 2064 ESPRIT patients (65%). The survey response rate was 91% (10 of 11) from Canadian sites and 58% (47 of 81) from US sites. In this smaller patient cohort, an association continued to be observed between enrollment in Canada and reduced ischemic complications after PCI. Canadian patients had reduced rates of 30-day (6.3% versus 10.3%; $P = 0.009$) and one-year death, MI or TVR compared with US patients (14.9% versus 20.1%; $P = 0.013$) (Figure 1).

Among survey participants, all Canadian sites were academic centres compared with a mixture of community and university-based hospitals in the US (Table 1). The median institutional volumes were similar over the two years that ESPRIT was conducted and were also similar among Canadian and US sites during this period. All sites reported that local glycoprotein IIb/IIIa inhibitor use markedly increased after the positive results of the ESPRIT trial became available.

The median age of physicians performing PCI was 47 years, with a median PCI experience of 13 years (Table 2). Canadian operators in ESPRIT had somewhat higher career PCI volumes than US operators ($P = 0.098$) and higher case volumes over the study period ($P = 0.008$ for the two-year averaged volume).

Using multivariate regression modelling, institutional volume was determined to be associated with a modest decline in 30-day and one-year death, MI or TVR (Table 3). Operator volume was not predictive of these outcomes in the dataset. Despite the addition of volume variables to the death, MI or TVR models, enrollment in Canada

remained highly predictive of improved clinical outcomes at 30 days and one year. Clinical outcomes were examined further according to operator volume (Table 4). Operators with annual case volumes of fewer than 100 cases per year showed a strong trend toward large MIs associated with their procedures.

DISCUSSION

Many US-based studies have reported a strong inverse relationship between annual PCI volumes performed by an individual physician or institution and clinical outcomes after PCI (1-6). This relationship has been confirmed during both the pre- and post-stent eras (4). The ESPRIT dataset suggests that procedural outcome after PCI is a function of institutional volume, but not operator volume. It is unclear whether higher institutional volumes are causative of the improved clinical outcomes, or simply a marker for other causal factors such as better established care pathways or increased use of evidence-based medicine. We originally hypothesized that Canadian and US centres participating in ESPRIT would be disparate in terms of operator volume, experience and institutional experience with PCI. The Canadian sites were all academic centres, while the US sites were a mixture of community and academic hospitals. However, Canadian and US sites in ESPRIT all had similar institutional volumes and highly experienced operators. The two volume variables did not explain the marked differences in clinical outcome among Canadian and US patients enrolled in the trial. Low operator volume (fewer than 100 cases per year) was associated with lower rates of thienopyridine pretreatment, decreased use of thienopyridine loading doses and increased rates of side branch closure, and may be associated with increased rates of large MIs following PCI.

Cantor et al (10) recently reported Ontario PCI outcomes. Their study failed to demonstrate a relationship between operator volume and outcome in Ontario because the vast majority of operators were performing well above 75 cases per year. We also encountered this situation in the ESPRIT trial. The improved clinical outcomes associated with enrollment in Canada could not be attributed to enhanced operator skill or institutional experience at Canadian sites relative to their US counterparts because the survey data indicated that ESPRIT sites were fairly homogeneous across North America for these variables.

Limitations

The institutions and operators assessed in the present trial, along with the patients who agreed to participate in a clinical trial, do not necessarily represent a cross-section of interventional practice in North America. Therefore, the observations from the present analysis may not be generalizable to other practice settings. Institutional and operator volumes were self-reported and not confirmed by independent sources. Previous publications examining volume-outcome relationships have used large Medicare or similar types of databases involving very large numbers of operators, institutions and

Figure 1) Kaplan-Meier survival curves showing the one-year incidence of death, myocardial infarction (MI) or target vessel revascularization (TVR), and the one-year incidence of death or MI, among the sites participating in the survey, stratified by country of enrollment. US United States

procedures. Thus, our study may have been underpowered to detect an operator volume-outcome relationship. Furthermore, the majority of operators in the ESPRIT trial were highly experienced by current standards, making it difficult to prove a volume-outcome relationship using this dataset. Finally, the response rate for the questionnaire was 62%. It is possible that patients from responding centres had characteristics that were different from those at centres that did not participate in the survey.

CONCLUSIONS

Among hospitals participating in the ESPRIT trial, institutional volume was associated with a modest (3%) reduction in the risk of death,

TABLE 1
Site data

	United States sites (n=47)	Canadian sites (n=10)	All sites (n=57)
Institution type, n (%)			
University	24 (51)	10 (100)	34 (60)
Community	21 (45)	0 (0)	21 (37)
Veterans Affairs hospital	2 (4)	0 (0)	2 (4)
Cardiologists performing PCI	8 (5-14)	5 (4-7)	8 (5-14)
Institutional volume in 1999 (cases)	1070 (550-1600)	1038 (970-1556)	1064 (559-1594)
Institutional volume in 2000 (cases)	1093 (600-1798)	1207 (1100-1700)	1199 (610-1780)
Glycoprotein IIb/IIIa inhibitor use before ESPRIT (% of PCI cases)	40 (20-65)	20 (10-25)	37 (20-50)
Glycoprotein IIb/IIIa inhibitor use after ESPRIT (% of PCI cases)	75 (60-90)	86 (50-90)	78 (60-90)

Data presented as median (interquartile range) unless otherwise specified. PCI Percutaneous coronary intervention; ESPRIT Enhanced Suppression of the Platelet glycoprotein IIb/IIIa Receptor with Integrilin Therapy trial

TABLE 2
Physician data

	United States MDs (n=133)	Canadian MDs (n=43)	All MDs (n=176)
Age, years	47 (42–52)	48 (43–55)	47 (42–52)
PCI experience, years	14 (10–17)	12 (8–17)	13 (10–17)
PCI volume in 1999 (cases)	200 (120–250)	228 (200–300)	200 (138–270)
PCI volume in 2000 (cases)	200 (135–300)	250 (200–300)	222 (150–300)
Career PCI volume (post fellowship)	1825 (1000–2800)	2000 (1485–3775)	2000 (1200–3000)
Routine use of glycoprotein IIb/IIIa inhibitor during PCI, n (%)	74 (64)	26 (67)	100 (65)

Data presented as median (interquartile range) unless otherwise specified. PCI Percutaneous coronary intervention; MD Physician

TABLE 3
Predictors of 30-day and one-year occurrence of death, myocardial infarction or target vessel revascularization

Variable	OR (95% CI)	P	Comment
30-day			
Institutional volume	0.97 (0.94–1.00)	0.058	OR for each 100-patient increase
Operator volume	1.02 (0.93–1.12)	0.69	OR for each 50-patient increase
Canadian patient	0.50 (0.37–0.68)	0.001	
Eptifibatide therapy	0.60 (0.39–0.91)	0.018	
Stable angina	0.68 (0.43–1.08)	0.10	
TIMI flow grade in index lesion pre-PCI	0.73 (0.59–0.92)	0.006	
Weight (kg)	0.99 (0.98–1.00)	0.15	
One-year			
Institutional volume	0.96 (0.94–0.99)	0.002	OR for each 100-patient increase
Operator volume	1.06 (0.98–1.14)	0.14	OR for each 50-patient increase
Canadian patient	0.66 (0.52–0.84)	0.001	

PCI Percutaneous coronary intervention; TIMI Thrombolysis In Myocardial Infarction

TABLE 4
Clinical outcomes by operator volume

	Operator case volume		P*
	<100 (n=91)	≥100 (n=1136)	
30-day			
Death/MI/urgent TVR	12 (13.2)	99 (8.7)	0.18
Death/MI	10 (11.0)	92 (8.1)	0.36
Death	1 (1.1)	6 (0.5)	0.53
MI	10 (11.0)	88 (7.8)	0.29
Large MI†	7 (7.7)	38 (3.3)	0.060
TVR	4 (4.4)	19 (1.7)	0.11
One-year			
Death/MI/any TVR	17 (18.9)	200 (17.9)	0.71
Death/MI	11 (12.1)	108 (9.6)	0.39
Death	3 (3.3)	15 (1.3)	0.13
MI	10 (11.0)	97 (8.6)	0.39
TVR	9 (9.9)	119 (10.5)	0.92

Data presented as n (%). *P-value from likelihood ratio χ^2 test at 30 days and log-rank test at one year. One-year event rates are Kaplan-Meier estimates;

†Creatine kinase-myocardial band ≥5 times the upper limit of normal. MI Myocardial infarction; TVR Target-vessel revascularization

MI or TVR over short- and long-term follow-up periods. The Canadian and US investigators and institutions selected in ESPRIT had quite similar annual procedural volumes. Therefore, volume variables could not explain the differential risk of clinical events observed among patients enrolled in the two countries.

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