Transfer for urgent percutaneous coronary intervention early after thrombolysis for ST-elevation myocardial infarction: The TRANSFER-AMI pilot feasibility study

Warren J Cantor MD^{1,2}, Jason Burstein MD³, Richard Choi MD⁴, Michael Heffernan MD PhD⁵, Vladimir Dzavik MD^{2,6}, Charles Lazzam MD⁷, Marko Duic MD⁴, David Fitchett MD^{2,8}, Mary Tan BSc⁹, Janet Wawrzyniak RN⁹, Saleem Kassam MD¹⁰, Sanjay Dhingra MD³, Laurie J Morrison MD^{2,11}, Anatoly Langer MD^{2,8,9}, Shaun G Goodman MD^{2,8,9}

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BACKGROUND: Most hospitals in Canada do not have percutaneous coronary intervention (PCI) facilities and use thrombolysis as reperfusion therapy for ST-elevation myocardial infarction (STEMI). Urgent PCI after thrombolysis may optimize reperfusion and prevent reinfarction and recurrent ischemia.

OBJECTIVE: To determine the feasibility of transferring high-risk STEMI patients from community hospitals in Ontario to PCI centres for urgent PCI within 6 h of thrombolysis.

METHODS: Patients with anterior or high-risk inferior STEMI received tenecteplase and were urgently transferred to PCI centres. PCI was performed if at least 70% stenosis was present in the infarct-related artery, regardless of flow, using coronary stents. Transfer of stable patients back to community hospitals was encouraged 24 h to 48 h after PCI.

RESULTS: Eighteen patients were transferred and underwent PCI a median of 3.9 h (range 2.7 h to 6.4 h) after thrombolysis. No complications occurred during transfer. One death occurred that was related to failed reperfusion and cardiogenic shock. Minor access-site bleeding occurred in five patients. Fifteen patients were transferred back to their community hospitals within 24 h of PCI. There were no further deaths or reinfarctions at one-year follow-up.

CONCLUSIONS: Transfer of high-risk STEMI patients for urgent PCI within 6 h after thrombolysis appears feasible. The randomized trial phase of the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) will compare this strategy with standard treatment after thrombolysis.

Key Words: Angioplasty; Clinical trials; Myocardial infarction, Thrombolysis

Le transfert pour subir une intervention coronaire percutanée peu après une thrombolyse en cas d'infarctus du myocarde par surélévation du segment ST : Le projet pilote de faisabilité TRANSFER-AMI

HISTORIQUE : La plupart des hôpitaux du Canada ne possèdent pas d'installations pour effectuer des interventions coronaires percutanées (ICP) et utilisent la thrombolyse comme traitement de reperfusion en cas d'infarctus du myocarde avec surélévation du segment ST (IMSSST). Une ICP d'urgence après une thrombolyse peut optimiser la reperfusion et prévenir un nouvel infarctus et une ischémie récurrente.

OBJECTIF : Déterminer la faisabilité de transférer les patients atteints d'un IMSSST à haut risque des hôpitaux généraux ontariens vers des centres d'ICP pour subir une ICP d'urgence dans les six heures suivant une thrombolyse.

MÉTHODOLOGIE : Les patients atteints d'un IMSSST antérieur ou inférieur à haut risque ont reçu de la ténecteplase et ont été transférés d'urgence à un centre d'ICP. L'ICP était effectuée en cas de sténose d'au moins 70 % de l'artère infarctée, quel que soit le débit, au moyen d'une endoprothèse coronarienne. Le transfert des patients stables vers leur hôpital général était encouragé de 24 heures à 48 heures après l'ICP.

RÉSULTATS : Dix-huit patients ont été transférés et ont subi une ICP selon une médiane de 3,9 heures (fourchette de 2,7 heures à 6,4 heures) après une thrombolyse. Aucune complication ne s'est produite pendant le transfert. Un décès a eu lieu, relié à l'échec de la reperfusion et à un choc cardiogène. Cinq patients ont subi une hémorragie mineure au foyer d'accès. Quinze patients ont été transférés à leur hôpital général d'origine dans les 24 heures suivant l'ICP. Aucun autre décès ou infarctus n'avait eu lieu au suivi d'un an.

CONCLUSIONS : Le transfert des patients atteints d'un IMSSST à haut risque afin de subir une ICP d'urgence dans les six heures suivant une thrombolyse semble faisable. La phase d'essai aléatoire de l'essai TRANSFER-AMI sur l'angioplastie systématique et l'endoprothèse après une fibrinolyse pour améliorer la reperfusion en cas d'infarctus aigu du myocarde permettra de comparer cette stratégie au traitement standard après une thrombolyse.

¹Southlake Regional Health Centre, Newmarket; ²University of Toronto, Toronto; ³Rouge Valley Ajax and Pickering, Ajax; ⁴St Joseph's Health Care Centre, Toronto; ⁵Oakville-Trafalgar Memorial Hospital, Oakville; ⁶Toronto General Hospital, Toronto; ⁷Trillium Health Centre, Mississauga; ⁸St Michael's Hospital; ⁹The Canadian Heart Research Centre, Toronto; ¹⁰Rouge Valley Centenary, Scarborough; ¹¹Sunnybrook Hospital, Toronto, Ontario

Correspondence: Dr Warren J Cantor, St Michael's Hospital, Division of Cardiology, 30 Bond Street, Toronto, Ontario M5B 1W8.

Telephone 416-864-5628, fax 416-864-5159, e-mail cantorw@smh.toronto.on.ca

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Patients with ST-elevation myocardial infarction (STEMI) need prompt restoration of coronary blood flow through the infarct-related artery (IRA) to minimize myocardial necrosis and improve chances of survival. The two strategies used in clinical practice are pharmacological reperfusion (using thrombolytic therapy) and mechanical reperfusion (using primary percutaneous coronary intervention [PCI]). Because most hospitals do not have on-site PCI capability, thrombolysis is the primary mode of reperfusion therapy for most centres in Canada (1). A third option is to administer thrombolytic therapy in community hospitals and transfer patients for urgent PCI to hospitals that perform PCI. This approach aims to optimize early infarct artery patency by combining pharmacological and mechanical reperfusion strategies, and prevents reocclusion, reinfarction and recurrent ischemia (2). This strategy of routine early PCI after thrombolysis may be most beneficial in higher risk STEMI patients.

The Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) pilot feasibility study was undertaken to determine the feasibility and safety of transferring patients presenting with high-risk STEMI from community hospitals in Ontario to regional PCI centres for urgent PCI within 6 h of thrombolysis.

METHODS

Study population

Patients with acute STEMI presenting to four community hospitals without onsite primary PCI capabilities in the greater Toronto area, Ontario, were screened for the study. Patients were eligible if they presented within 12 h of symptom onset with chest pain more than 30 min in duration and ST-segment elevation of 2 mm or more in the anterior leads or 1 mm or more in the inferior leads. In addition, inferior STEMI patients were required to have one of the following: systolic blood pressure lower than 100 mmHg; heart rate of higher than 100 beats/min; Killip class II or III; 2 mm or more of ST-segment depression in the anterior leads; or 1 mm or more of ST-segment elevation in the right-sided lead position V4, indicative of right ventricular involvement. Exclusion criteria included left bundle branch block, cardiogenic shock, time from thrombolysis to consent greater than 30 min, use of a fibrinolytic agent other than tenecteplase, PCI within one month, previous bypass surgery, or availability of primary PCI with an anticipated door-to-balloon time of less than 60 min. Patients were not enrolled if no coronary care unit (CCU) beds were available at participating PCI centres or if transfer to the PCI centre was expected to be delayed more than 6 h. Enrolment was carried out during off-hours and during daytime working hours. All patients provided informed consent before enrolment. The protocol was approved by the institutional research ethics committee of each participating hospital.

Interventions

All patients were treated with tenecteplase. For patients 75 years of age or younger, either unfractionated heparin or enoxaparin was used based on the standard regimen at participating centres. For patients older than 75 years of age, only unfractionated heparin was permitted. All patients received acetylsalicylic acid at the time of thrombolysis. Clopidogrel was administered as a 300 mg bolus given either immediately before or immediately after coronary stenting, followed by 75 mg daily for a minimum of one

month. All other cardiac medications, including beta-blockers, angiotensin-converting enzyme inhibitors and lipid-lowering drugs, were used as clinically required, consistent with published guidelines for STEMI (3). Patients were transferred to one of three participating PCI centres. Ambulance transfers were provided by a single ambulance service employing critical care transfer units staffed by paramedics with advanced life support and critical care skills. Coronary angiography was performed as soon as possible after arrival at the PCI centre. Following angiography, all patients with residual stenosis of at least 70% in the IRA underwent PCI, regardless of patency or flow in the IRA. Intervention of non-IRAs during the same procedure was strongly discouraged. Stents were used whenever technically possible, and Guidant stents (Guidant Canada) were preferred. Glycoprotein (GP) IIb/IIIa inhibitor use at the time of PCI was left to the discretion of the interventional cardiologist. Femoral sheaths were removed 4 h after intervention if no vascular closure device was used. Radial sheaths were removed immediately after the procedure. If clinically stable, patients were transferred back to referral centres within 24 h to 48 h after PCI. Patients were seen for follow-up at 30 days and contacted by telephone at six months and one year.

End points

Potential clinical efficacy end points included death, reinfarction, severe recurrent ischemia, new or worsening heart failure or cardiogenic shock. Reinfarction within the first 18 h was defined as recurrent ST elevation and recurrent chest pain lasting at least 30 min. After 18 h, the diagnosis of reinfarction required a rise in creatine kinase (muscle and brain) (CK-MB) greater than the upper limit of normal (ULN) (greater than three times ULN after PCI and greater than five times ULN after coronary artery bypass grafting) or new Q waves on the electrocardiogram. If the CK-MB had not yet normalized, then reinfarction after 18 h required re-elevation of the CK-MB levels by at least 50% over the previous value. Recurrent ischemia was defined as chest pain lasting at least 5 min associated with electrocardiographic ST segment or T wave changes consistent with acute ischemia. New or worsening heart failure was defined as heart failure requiring treatment 6 h or more after enrolment and either pulmonary edema on chest x-ray, or rales greater than one-third of the way up the lung fields on chest auscultation or pulmonary capillary wedge pressure greater than 18 mmHg. Cardiogenic shock was defined as persistent systolic blood pressure of less than 90 mmHg without inotropic support, or that requiring inotropic support to maintain systolic blood pressure at more than 90 mmHg, associated with clinical evidence of hypoperfusion. Possible safety end points included bleeding complications, classified by the Thrombolysis In Myocardial Infarction (TIMI) (4) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) (5) bleeding severity scales, stroke and life-threatening complications (eg, arrhythmia, respiratory arrest, hypotension) during transfer. Feasibility was evaluated by the ability to transfer patients to the PCI centre and perform PCI within 6 h of thrombolysis.

Statistical analysis

The present study was designed as an exploratory pilot study to determine the feasibility for a larger definitive randomized trial. Baseline, procedural and angiographic characteristics were summarized as medians, with range values for continuous measures and percentages for discrete measures. No inferential statistical analyses were performed.

TABLE 1
Baseline clinical characteristics (n=20)

Age, years	60 (38–77)
Female, n (%)	4 (20)
Weight, kg	85 (41–132)
Diabetes, n (%)	6/18 (33)
Hypertension, n (%)	7/19 (37)
Currently smoking, n (%)	8/19 (42)
Hyperlipidemia, n (%)	5 (25)
Heart rate, beats/min	86 (60–120)
Systolic blood pressure, mmHg	138 (90–210)
Killip class I, n (%)	15 (75)
Killip class II, n (%)	5 (25)
Anterior ST elevation, n (%)	16 (80)
Inferior ST elevation, n (%)	4 (20)
Heart rate >100 beats/min	0
Systolic blood pressure <100 mmHg, n (%)	2 (10)
≥2 mm ST depression in anterior leads	0
≥1 mm ST elevation V ₄ R, n (%)	2 (10)

Age, weight, heart rate and systolic blood pressure are expressed as mean (range). V₄R Right-sided lead in position V4

RESULTS

Baseline characteristics

Twenty patients were enrolled in the pilot phase of the TRANSFER-AMI study between November 2003 and January 2004. The four enrolling sites and three PCI centres are listed in the Appendix. Three patients were not enrolled due to the lack of available CCU beds at the PCI centres. Baseline clinical characteristics are shown in Table 1. Two patients were excluded after enrolment and transfer to the PCI centre, and angiography was not performed. One of these patients was recognized as having an acute aortic dissection and was sent emergently for surgery. This patient had a prolonged and complicated postoperative course in the intensive care unit and died four months later. The other patient successfully reperused with thrombolysis and declined cardiac catheterization.

Time intervals

The median time from tenecteplase administration to arrival at the cardiac catheterization laboratory was 3.3 h (range 2.3 h to 5.6 h). The median time from tenecteplase administration to first balloon inflation was 3.9 h (range 2.7 h to 6.4 h). The detailed breakdown of time intervals is shown in Table 2.

Transfer data

The median transport distance between referral and PCI centres was 7.1 km, with a range of 6.8 km to 47.6 km. There were no complications during transfer to the PCI centres.

Angiographic and PCI characteristics

PCI was attempted in all 18 patients. Successful reperfusion (TIMI grade 2 or 3 flow after PCI) was achieved in 17 patients. One patient had persistent occlusion of both the left anterior descending and left circumflex coronary arteries after thrombolysis, and antegrade flow in the left anterior descending artery could not be restored despite angioplasty, thrombectomy, intracoronary thrombolysis and GP IIb/IIIa inhibitor administration. The patient developed cardiogenic shock and

TABLE 2
Pilot study time intervals in hours

	Median, h	Range
Symptom onset to hospital presentation	1.9	0.5–9.1
Hospital presentation to TNK	0.5	0.3–1.5
TNK to ambulance departure	1.7	0.8–3.9
Ambulance departure to arrival at PCI centre	0.5	0.1–1.4
Arrival at PCI centre to catheterization laboratory	0.7	0.03–2.3
Catheterization laboratory to first balloon inflation	0.7	0.2–1.1
TNK to arrival in catheterization laboratory	3.3	2.3–5.6
TNK to first balloon inflation	3.9	2.7–6.4
Symptom onset to first balloon inflation	6.7	4.0–13.5

PCI Percutaneous coronary intervention; TNK Tenecteplase

TABLE 3
Angiographic findings (n=18)

Infarct-related artery, n (%)	
Left anterior descending	14 (78)
Circumflex coronary	0
Right coronary	4 (22)
Baseline TIMI flow of infarct-related artery, n (%)	
0	3 (17)
1	2 (11)
2	5 (28)
3	8 (44)
Baseline % stenosis of infarct-related artery, median (range)	90 (70–100)
Single-vessel CAD, n (%)	9 (50)
Double-vessel CAD, n (%)	7 (39)
Triple-vessel CAD, n (%)	2 (11)

CAD Coronary artery disease; IRA Infarct-related artery; TIMI Thrombolysis In Myocardial Infarction

underwent placement of an intra-aortic balloon pump followed by a left ventricular assist device and emergency bypass surgery; he remained in cardiogenic shock and died several days later. The baseline angiographic data are shown in Table 3. Eight patients (44%) had TIMI grade 3 flow before PCI. All patients with TIMI grade 2 or 3 flow had stenoses of 70% or more in the IRA. After PCI, 15 (83%) patients had TIMI grade 3 flow. No patient had a worse TIMI flow grade after PCI. All 18 patients received GP IIb/IIIa inhibitors and 17 (94%) received stents. The GP IIb/IIIa inhibitors were started 3.8 h (range 2.9 h to 5.4 h) after thrombolysis. Femoral access was used for nine patients and radial access was used for the remaining nine patients. No significant complications occurred in the catheterization laboratory other than minor dissections treated with stenting (Table 4). No patients developed 'no reflow' or distal embolization after PCI.

Hospital length of stay and repatriation

The median lengths of stay were one day (range zero to 18 days) at the PCI centres, three days (range two to 12 days) at the referring community hospital and five days (range three to 18 days) at both hospitals combined. Fifteen patients (83%) were transferred back to the referring community hospital at a median of 24 h (range 14 h to 93 h) after PCI. No complications occurred during or after transfer back to the community hospitals.

TABLE 4
Procedural characteristics (n=18)

	n (%)
Glycoprotein IIb/IIIa use	18 (100)
Abciximab	14 (78)
Eptifibatide	4 (22)
Coronary stents	17 (94)
Distal protection device	1 (6)
Thrombectomy device	1 (6)
Radial access	9 (50)
Femoral access	9 (50)
Complications	
Minor dissection	2 (11)
Final TIMI flow of infarct-related artery	
TIMI 0–1	1 (6)
TIMI 2	2 (11)
TIMI 3	15 (83)

TIMI Thrombolysis In Myocardial Infarction

Clinical events

The clinical events during the initial hospitalization are listed in Table 5. Among the 18 patients, there was one death (described above). The composite end point of death, cardiogenic shock, heart failure and recurrent ischemia occurred in seven patients. Two patients required bypass surgery (one emergent, one elective). Bleeding complications occurred in six patients. There were five TIMI minor bleeding complications at the arterial access site and one case of a TIMI major bleed related to elective bypass surgery performed 11 days after PCI. Access-site bleeding occurred in four of the transfemoral procedures and one of the transradial procedures ($P=0.1$). Two patients required blood transfusions. Between hospital discharge and 30 days, one patient had undergone staged PCI of a non-IRA, but there were no other events. No deaths or reinfarctions occurred between 30 days and one year.

DISCUSSION

In the present pilot study, we demonstrated the feasibility of transferring patients with acute STEMI from community hospitals in the greater Toronto area to regional PCI centres for urgent PCI within 6 h of thrombolysis. There were no complications during transfers, and no major bleeding related to the PCI procedure was seen despite the use of GP IIb/IIIa inhibitors after full-dose thrombolysis in all patients. Major in-hospital adverse cardiac event rates were consistent with the clinical profiles of high-risk STEMI patients enrolled in this study. Most patients were transferred back to their community hospitals approximately 24 h after PCI.

Patients with acute STEMI require rapid reperfusion therapy with either thrombolysis or primary PCI to minimize infarct size and reduce morbidity and mortality. Primary PCI is associated with lower rates of death, reinfarction and stroke when performed in a timely manner (6,7). However, treatment delays can reduce or eliminate the benefits of primary PCI (8). Current STEMI guidelines recommend a door-to-balloon time of 90 min or less, which is not achieved in many North American hospitals, particularly when transfer to a PCI centre is required (1,3,9). Consequently, thrombolysis remains the standard-of-care for STEMI in most Canadian hospitals (1). Thrombolysis fails to restore IRA patency within 90 min in

TABLE 5
Clinical outcomes during initial hospitalization

	n (%)
Death	1 (6)
Cardiogenic shock	2 (11)
New or worsening heart failure	3 (17)
Recurrent ischemia	4 (22)
Recurrent myocardial infarction	0
Suspected stroke/transient ischemic attack	0
Repeat percutaneous coronary intervention	0
Coronary artery bypass surgery	2 (11)
TIMI major bleeding	1 (6)
TIMI minor bleeding	5 (28)
GUSTO severe bleeding	0
GUSTO moderate bleeding	3 (17)
GUSTO mild bleeding	3 (17)

GUSTO Global Use of Strategies to Open Occluded Coronary Arteries; TIMI Thrombolysis In Myocardial Infarction

approximately 20% of patients and achieves TIMI grade 3 flow in less than 60% of patients (10). Over 20% of patients with TIMI grade 3 flow have absent myocardial perfusion at the tissue level (11). Even after successful thrombolysis, patients remain at risk for reocclusion, reinfarction and recurrent ischemia.

Routine early PCI after thrombolysis has been proposed as a strategy to optimize early reperfusion and prevent reinfarction and recurrent ischemia. Studies carried out before the use of coronary stents showed no benefit of routine early PCI after thrombolysis (12). In more recent studies (13–15) using contemporary PCI techniques (including coronary stenting) and pharmacotherapy, patients treated with early PCI after thrombolysis had improved clinical outcomes with no excess of major bleeding complications. These positive results contributed to the recommendation of routine coronary angiography after thrombolysis in the most recent European guidelines (16). However, these trials have been too small to provide definitive conclusions regarding the safety and efficacy of this approach. The Canadian Which Early ST-elevation myocardial infarction Therapy (WEST) study randomly assigned 304 STEMI patients to tenecteplase alone, tenecteplase and cardiac catheterization (and PCI, if required) within 24 h, or primary PCI. The trial emphasized the diagnosis of STEMI and random assignment in the prehospital setting. The preliminary results were recently presented and demonstrated similar outcomes in all three treatment groups (17). However, this pilot trial was underpowered to establish equivalence among treatment strategies. In the fourth ASessment of the Safety and Efficacy of a New Treatment strategy for acute myocardial infarction (ASSENT-4) trial, 1667 STEMI patients were randomly assigned to primary PCI versus tenecteplase, followed by PCI at a median of 104 min after thrombolysis (18). Primary PCI was associated with significantly lower 30-day mortality, although the differences were not statistically significant after risk adjustment. There was also a significantly lower rate of stroke associated with primary PCI. The ASSENT-4 results highlight the ongoing uncertainty regarding the need for, and optimal timing of, routine PCI after thrombolysis. Ongoing trials, including TRANSFER-AMI and Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE),

Figure 1) Study design of the Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) randomized trial. Cath Catheterization; CHF Congestive heart failure; ECG Electrocardiogram; Echo Echocardiogram; GP Glycoprotein; MI Myocardial infarction; PCI Percutaneous coronary intervention

will provide important insights on the pharmacoinvasive treatment strategy.

The TRANSFER-AMI trial was designed to compare the strategy of routine early PCI, performed urgently within 6 h of thrombolysis, with standard care after thrombolysis (Figure 1) (19). Rescue PCI was shown to improve clinical outcomes in the Rapid Early Action for Coronary Treatment (REACT) trial, and is mandated by protocol for TRANSFER-AMI patients randomly assigned to standard care who have evidence of failed reperfusion. In contrast to ASSENT-4, the TRANSFER-AMI study strongly encourages upfront clopidogrel and PCI is performed several hours after thrombolysis, with liberal use of GP IIb/IIIa inhibitors. In ASSENT-4, heparin was administered as a single bolus only, with no infusion (which may account for the lower than expected TIMI grade 3 flow rate after tenecteplase), whereas in TRANSFER-AMI, patients receive a heparin bolus and infusion or enoxaparin. Patients enrolled in TRANSFER-AMI are generally not eligible for primary PCI due to the delays imposed by long transport times.

Regardless of whether patients are treated with primary PCI, thrombolysis or a combined approach, time to treatment is a critical determinant of outcomes. The rapid initiation of therapy in the WEST trial was associated with very low mortality rates in all three treatment groups (17). The long transfer times seen in the present pilot study demonstrate the challenges in providing timely interhospital transfers in large urban centres, and are related, in part, to limited ambulance availability.

Before commencing the randomized phase of TRANSFER-AMI, the present pilot study was carried out to determine the feasibility of transferring patients from community hospitals to PCI centres to undergo urgent coronary angiography and PCI within 6 h of thrombolysis. No complications occurred during

transfer, which is consistent with other studies (6,20) that demonstrated a very low incidence of serious complications during transfer of STEMI patients. We have also demonstrated the safety and feasibility of early repatriation to community hospitals for the majority of patients after successful PCI. Early repatriation may be necessary at many PCI centres to maintain CCU bed availability and the ability to accept additional patients in transfer.

CONCLUSIONS

Transfer of patients with STEMI for urgent PCI within 6 h of thrombolysis is feasible. The larger ongoing TRANSFER-AMI randomized trial will compare the safety and efficacy of this strategy with standard treatment after thrombolysis in 1200 high-risk STEMI patients.

APPENDIX

Participating centres

Community hospitals

St Joseph's Health Care Centre, Toronto, Ontario – Dr Richard Choi,
Dr Marko Duic, Darlene Wilkinson, Joan Sinclair
Oakville-Trafalgar Memorial Hospital, Oakville, Ontario – Dr Michael Heffernan,
Dr Lorne Martin, Rebecca Franks
Rouge Valley Centenary, Scarborough, Ontario – Dr Saleem Kassam,
Brenda Hart, Bev Bozek
Rouge Valley Ajax and Pickering, Ajax, Ontario – Dr Sanjay Dhingra,
Dr Gary Mann, Carrie Harrison, Theresa Eyman

Angioplasty centres

St Michael's Hospital, Toronto, Ontario – Dr Warren J Cantor, Anne Fry
Toronto General Hospital, Toronto, Ontario – Dr Vladimir Dzavik,
Deborah Atchison
Trillium Health Centre, Mississauga, Ontario – Dr Charles Lazzam,
Arlene Carter

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