Canadian Agency for Drugs and Technologies in Health
Health Technology Inquiry Service
Health Technology Assessment HTA

TITLE: **Left Atrial Appendage Occlusion: Cost-Effectiveness in a Canadian Setting**

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CONTEXT AND POLICY ISSUES:

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, associated with high morbidity and mortality.[1,2] AF increases the risk of clot formation and stroke four- to five-fold across all age groups and is responsible for 10% to 15% of all ischemic strokes.[3] AF is the most common cause of stroke among the elderly, representing approximately 25% of strokes in patients age ≥ 80 years.[4]

Oral anticoagulants are currently used as the standard treatment to prevent stroke in AF patients. [5] These drugs have been shown to reduce the risk of thromboembolic events by 68 percent.[6] Despite the high efficacy of oral anticoagulants there are some concerns associated with the use of these drugs such as increased risk of bleeding and need for regular control of the International Normalized Ratio (INR). Furthermore, anticoagulation is contraindicated or considered to be risky in patients with hemorrhagic tendencies, acute pericarditis, or recent planned surgery of the eye or central nervous system, as well as in pregnant patients and those who are at an increased risk of a fall.[7,8]

In about 90% of AF patients stroke originates from thrombotic embolization due to the loss of atrial appendage contractility and emptying.[9,10] Therefore, closure of the left atrial appendage (LAA) has been suggested as an alternative to anticoagulant therapy for stroke prevention in AF patients. Different approaches have been utilized for exclusion of LAA from circulation: surgical ligation and or amputation of LAA in patients who undergo valvular open heart surgeries, thoracoscopic exclusion of LAA using an endoloop snare or staple, and percutaneous catheter-based procedures.[11-13]

Several percutaneous catheter-based devices exist, including the PLAATO system (EV3 Endovascular, Inc. North Plymouth, MN, USA), the Watchman device (Atritech, Inc. North Plymouth, MN, USA), the Transcatheter Patch (Custom Medical Devices, Athens, Greece), and the Amplatzer Cardiac Plug (ACP) (AGA medical Corp., North Plymouth, MN, USA).[13] The feasibility and efficacy of LAA closure using these devices have been shown in clinical studies.[14-19]

The ACP device is available in Canada and is approved for special access. This device is made of flexible braided Nitinol mesh and consists of a plug and proximal disk connected by a flexible central waist. Plug size ranges from 16 to 30 mm and the disk size varies between 20 - 36 mm. The ACP is delivered using a 9F venous sheath in the smallest size and a 13F sheath in the largest size, under fluoroscopic and transesophageal echocardiography guidance.

In addition to evidence on clinical benefit, funding decision making bodies may need to consider the value for money of the procedure.

RESEARCH QUESTION:

What is the cost-effectiveness of percutaneous occlusion of the left atrial appendage for patients with non-valvular atrial fibrillation at elevated risk for stroke in a Canadian setting?

METHODS:

Literature search

This report is based upon studies retrieved for a previous CADTH report: Ablation Procedures for Rhythm Control in Patients with Atrial Fibrillation: Clinical and Cost-Effectiveness Analyses.[20]

Overview

A cost-utility analysis was undertaken to compare two treatment strategies for patients with non-valvular atrial fibrillation who cannot tolerate long term warfarin therapy. The two strategies were:

1) Left Atrial Appendage (LAA) Occlusion
2) No treatment.

A Markov model was used to estimate the expected costs, strokes and quality adjusted life years (QALYs) for each treatment group over a 5 year time horizon. The starting cohort was assumed to be 65 year old males with a $CHADS_2$[21] stroke risk score of 2.5. This was based on the average $CHADS_2$ score in a registry study evaluating LAA occlusion for patients with AF at high risk of stroke.[15] The analysis was taken from the perspective of a provincial Ministry of Health. Costs from this perspective include drugs covered by the provincial formularies for eligible patients, inpatient costs, and physician fees for services covered by provincial fee schedules. Indirect costs, such as productivity losses, were not considered in the analysis. Costs and quality adjusted life years were discounted at 5% annually.

The Markov model was based on an adaption of a model evaluating AF ablation.[20] A recent CADTH review on LAA occlusion[22] was used to identify studies with clinical data relevant to the model.

Model Structure

A graphical representation of the model structure is provided in Figures 1 and 2. Figure 1 presents the structure for the LAA occlusion strategy for the first 3 month cycle of the model. As shown, a proportion of patients undergoing LAA occlusion incur the following periprocedural complications: death; ischemic stroke; and pericardial effusion. A proportion of patients who do not have a procedural complication will suffer a stroke during the initial 3 month cycle, while the remainder is stroke free.

Figure 2 presents the general structure of the model for both the no treatment strategy and the LAA occlusion strategy after the first 3 month cycle of the model. Patients can be in four mutually exclusive health states in each model cycle. Patients transition between these four health states each model cycle. Patients in the no stroke health state can transition to the stroke 1st year health state, can remain in the no stroke health state or can die. Patients in stroke 1st year health state transition to the stroke subsequent years health state if they remain alive after one year. Patients in stroke subsequent years health state remain in that health state for each cycle unless they die and transition to the dead health state. Health care costs, increased risk of death and a decrease in quality of life (utility values) are applied to patients in the stroke 1st year and stroke subsequent year health states.

Figure 1: Graphical representation of the structure of the first model cycle for LAA occlusion

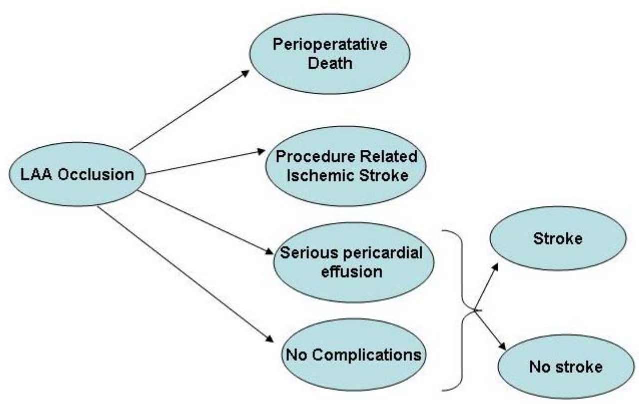
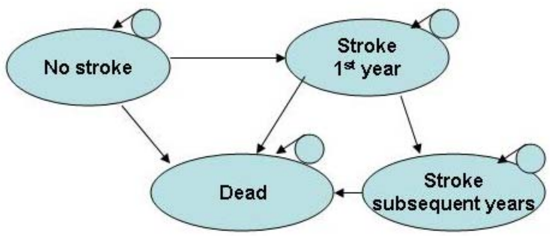


Figure 2: Graphical representation of general structure of model



Model Parameters

A number of model parameters were used to populate the model. These include the annual probability of stroke, stroke reduction after LAA occlusion, general population mortality rates, stroke mortality rates, general population utility values, utility weights associated with stroke, probability of procedural complications, the cost of the LAA occlusion procedure, the costs associated with procedural complications, and the costs related to stroke. The values and sources used for these variables are described below.

Probability of stroke

The probability of ischemic stroke for patients in the No Treatment strategy was based upon the $CHADS_2$ classification system published by Gage et al.[23] based on a $CHADS_2$ score of 2.5 the annual probability of stroke can be estimate to be 0.0495.

It was assumed that stroke reduction after LAA occlusion strategy is the same as the stroke reduction associated with warfarin treatment. This assumption was based upon a randomized controlled non-inferiority trial comparing the procedure to warfarin treatment.[19] Based on study findings, the authors concluded that LAA occlusion was non-inferior to warfarin. This was one of only two identified RCTs that have evaluated LAA occlusion. The other RCT evaluated LAA occlusion as an adjunct to coronary bypass.[24]

A meta-analysis by Hart et al.[21] estimated the relative risk reduction of stroke for individuals with non-valvular AF on warfarin compared to individuals on no treatment or placebo to be 0.64. This is equivalent to a relative risk of stroke of 0.36. This relative risk (0.36) was assumed for the LAA occlusion arm of the model.

Probability of periprocedural complications

In order to estimate the probability of periprocedural complications, data was pooled from all studies reporting adverse events after LAA occlusions. Studies evaluating LAA occlusion at the same time as other cardiac procedures were excluded. As shown in Table 1, the probability of procedure related stroke, serious pericardial perfusion and death was estimated to be 0.0074, 0.0387, and 0.0015, respectively.

Table 1: Data used to estimate probability of periprocedural complications				
Study	n	Procedural Related Stroke	Serious Pericardial Effusion	Death
Sick[18]	75	0	2	0
Holmes[19]	463	5	22	0
Meier[17]	12	0	0	0
Ostermayer[15]	111	0	1	1
Omran[25]	9	0	0	0
Barbato[26]	1	0	0	0
Stollberger[26]	1	0	1	0
Total	672	5	26	1
Probability of periprocedural complications		0.0074	0.0387	0.0015

Mortality rates

General population age and gender specific mortality rates, based upon Canadian Life Tables,[27] were applied to patients in the model in the absence of events (ischemic stroke, major bleeds). Based upon data reported in two Canadian based studies,[28,29] mortality in the first year following stroke was estimated to be 0.206 and 0.395 for males aged 65-79 and 80+, respectively. For post-stroke mortality after one year, general population mortality was increased by a factor of 2.3.[30]

Utilities

Patients free from stroke were assigned age and gender specific general population utility values.[31] Data from two studies were used to derive stroke health state utility weights. Riviero-Arias et al.[32] provided estimates of post stroke utility scores according to modified Rankin Score (mRS). In a Canadian based cohort study, Goeree et al.[33] reported the distribution of discharge modified ranking score according to type of stroke (ischemic, haemorrhagic, transient ischemic attack). Based on this data the utility weight applied to patients post stroke was 0.46.

Costs

The cost per LAA procedure was estimated to be $10,987.93. This estimate was comprised of hospital costs ($10,287.93) The cost per LAA procedure was estimated to be $10,987.93. This estimate was comprised of hospital costs ($10,287.93) (Jeff Coleman, Vice President, Regional Programs and Service Integration, Vancouver Coastal Health, Vancouver, BC: personal communication, 2010 Oct 5) and physician fees associated with the procedure ($700).[34] Hospital procedural costs included device and other supply costs, cardiac catherterization lab costs, along with the cost of an overnight stay in hospital. In the absence of a specific physician billing code for LAA occlusion in BC, the physician fees a *S33073 Percutaneous transcatheter cardiac* *occluder device closure of ASD – for patients over 18 years of age – composite fee was used.* [34]

The cost of stroke was estimated from a Canadian based costing study by Goeree et al.[33] In this study the total one year health care costs for patients suffering an ischemic stroke was found to be $53,576. Costs for the second year and beyond post stroke were assumed to be equal to the sum of the costs for: long term care, home care, prescription medications, outpatient visits, doctor visits and assistive devices. These cost amounted to $6,265. Using the Ontario Case Costing Initiative database, the cost of a serious myocardial perfusion was estimated to be $10,728.[35]

SUMMARY OF FINDINGS:

Table 3 provides the cost-effectiveness results using the basecase assumptions. Over a 5 year time horizon the model estimated LAA occlusion to have $5,240 more expected costs than no treatment. The model also predicted that LAA occlusion would avoid 0.125 strokes and result in 0.131 more expected QALYs compared to no treatment. The resulting incremental cost-utility ratio for LAA occlusion compared to no treatment is $40,229 ($5,270/0.131). Therefore based on the basecase analysis, if a decision makers' willingness to pay for a QALY is $40,229 or higher, LAA occlusion would be considered a cost effective strategy. Otherwise, no treatment is the cost-effective strategy.

Table 2: Basecase cost-effectiveness results

Treatment	Expected Costs	Expected Strokes	Expected QALYs	$/QALY
LAA Occlusion	$15,950	0.090	3.277	
No Treatment	$10,681	0.215	3.146	
Incremental (LAA Occlusion-no treatment)	$5,270	-0.125	0.131	$40,229

Table 3 presents the model results varying a number of key model parameters in one way sensitivity analyses. As shown, higher stroke risk defined by the $CHADS_2$ score results in more favourable cost effectiveness results. If patients have a $CHADS_2$ score of 3 instead of 2.5 the cost per QALY of LAA occlusion becomes $26,617. If patients have a $CHADS_2$ score of 4 the cost per QALY becomes $6,415. The cost-effectiveness of LAA occlusion becomes more favorable with increasing time horizons. If a 10 or 20 year time horizon is taken, LAA becomes both less costly than no treatment and more effective in terms of both strokes and QALYs. If the treatment effect of LAA occlusion is assumed to be less than that of warfarin compared to placebo, the cost-effectiveness of LAA occlusion becomes less favourable. If the relative risk of stroke is assumed to be 0.60 the cost per QALY of LAA occlusion becomes $107,329. Hart et al[21] estimated the relative risk reduction of warfarin compared to aspirin to be 0.38 which is equivalent to a relative risk of 0.62. Therefore, if it was assumed that the comparator group was on aspirin therapy instead of no anti-thrombotic therapy, the cost per QALY of LAA occlusion would approximate $107,329.

Table 3: One way Sensitivity analyses					
		Incremental (LAA occlusion-No treatment)			
		Expected Costs	Expected Strokes	Expected QALY's	Cost per QALY
$CHADS_2$					
	0	$9,164	-0.048	0.040	$226,392
	1	$7,954	-0.072	0.068	$116,804
	2	$6,420	-0.103	0.104	$61,980
	3	$4,173	-0.146	0.157	$26,617
	4	$1,435	-0.198	0.224	$6,415
Time horizon					
	3	$7,907	-0.079	0.050	$158,193
	5	$5,270	-0.125	0.131	$40,229
	10	-$163	-0.206	0.392	dominates
	20	-$5,870	-0.269	0.780	dominates
RR of stroke LAA occlusion					
	0	$1,213	-0.208	0.221	$5,480
	0.2	$3,502	-0.161	0.170	$20,563
	0.4	$5,703	-0.116	0.121	$47,182
	*0.6	$7,818	-0.074	0.073	$107,239
	0.8	$9,850	-0.033	0.026	$373,513

* approx relative risk of stroke for warfarin vs. aspirin

Limitations

There are a number of limitations on this analysis. No comparative study was identified that compared LAA occlusion with no treatment in patients with AF at high risk of stroke who can not tolerate warfarin therapy. Based upon a trial that found LAA occlusion to be non-inferior to warfarin treatment, the treatment effect of LAA occlusion was assumed to be the same as warfarin versus no treatment. The validity of this assumption may be questionable. Another limitation is that clinical studies used to inform this analysis were based upon different occlusion devices than the one that is available for use in Canada (ACP). Finally, indirect costs were not considered in the analysis.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In a reference case of 65 year old males with a $CHADS_2$ stroke risk score of 2.5, the incremental cost per quality adjusted life year gained for LAA occlusion compared to no treatment was estimated to be $40,229. Though no strict willingness to pay threshold exists in Canada, an intervention with this cost per QALY would generally be considered reasonably cost-effective. However, the cost-effectiveness results are highly dependant on the treatment effect assumed for LAA occlusion. If the comparator group in the analysis was assumed to be on aspirin treatment instead of no treatment, the relative risk of stroke for LAA occlusion would have been assumed to be around 0.60 instead of

0.36. Under this scenario, the cost per QALY of LAA occlusion would is estimated to be $107,239. An intervention with a cost per QALY of $107,239, may be perceived as being cost-ineffective.

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REFERENCES:

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001 May 9;285(18):2370-5.

2. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995 May;98(5):476-84.

3. Lip GY, Boos CJ. Antithrombotic treatment in atrial fibrillation. Heart. 2006 Feb;92(2):155-61.

4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991 Aug;22(8):983-8.

5. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006 Aug 15;114(7):e257-e354.

6. Rockson SG, Albers GW. Comparing the guidelines: anticoagulation therapy to optimize stroke prevention in patients with atrial fibrillation. J Am Coll Cardiol. 2004 Mar 17;43(6):929-35.

7. Bradley BC, Perdue KS, Tisdel KA, Gilligan DM. Frequency of anticoagulation for atrial fibrillation and reasons for its non-use at a Veterans Affairs medical center. Am J Cardiol. 2000 Mar 1;85(5):568-72.

8. Brass LM, Krumholz HM, Scinto JM, Radford M. Warfarin use among patients with atrial fibrillation. Stroke. 1997 Dec;28(12):2382-9.

9. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg. 1996 Feb;61(2):755-9.

10. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol. 1995 Feb;25(2):452-9.

11. Blackshear JL, Johnson WD, Odell JA, Baker VS, Howard M, Pearce L, et al. Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. J Am Coll Cardiol. 2003 Oct 1;42(7):1249-52.

12. Syed TM, Halperin JL. Left atrial appendage closure for stroke prevention in atrial fibrillation: state of the art and current challenges. Nat Clin Pract Cardiovasc Med. 2007 Aug;4(8):428-35.

13. Singh IM, Holmes DR, Jr. Left atrial appendage closure. Curr Cardiol Rep. 2010 Sep;12(5):413-21.

14. Ussia GP, Mangiafico S, Privitera A, Mule M, Caruso E, Galassi AR, et al. Percutaneous left atrial appendage transcatheter occlusion in patients with chronic nonvalvular atrial fibrillation: early institutional experience. J Cardiovasc Med (Hagerstown). 2006 Aug;7(8):569-72.

15. Ostermayer SH, Reisman M, Kramer PH, Matthews RV, Gray WA, Block PC, et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials. J Am Coll Cardiol. 2005 Jul 5;46(1):9-14.

16. Park JW, Leithauser B, Gerk U, Vrsansky M, Jung F. Percutaneous left atrial appendage transcatheter occlusion (PLAATO) for stroke prevention in atrial fibrillation: 2-year outcomes. J Invasive Cardiol. 2009 Sep;21(9):446-50.

17. Meier B, Palacios I, Windecker S, Rotter M, Cao QL, Keane D, et al. Transcatheter left atrial appendage occlusion with Amplatzer devices to obviate anticoagulation in patients with atrial fibrillation. Catheter Cardiovasc Interv. 2003 Nov;60(3):417-22.

18. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2007 Apr 3;49(13):1490-5.

19. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009 Aug 15;374(9689):534-42.

20. Assasi N, Blackhouse G, Xie F, Gaebel K, Robertson D, Hopkins R, et al. Ablation procedures for rhythm control in patients with atrial fibrillation: clinical and cost-effectiveness analyses [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010. (Technology report; no. 128) [cited 2010 Sep 29]. Available from: http://www.cadth.ca/index.php/en/hta/reports-publications/search/publication/2663

21. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007 Jun 19;146(12):857-67.

22. Health Technology Inquiry Service. Left atrial appendage occlusion for stroke prevention: clinical benefit [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010. [cited 2010 Sep 29]. Available from:

http://www.cadth.ca/media/pdf/k0257_left_atrial_appendage_occlusion_htis-1-5.pdf

23. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001 Jun 13;285(22):2864-70.

24. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. Am Heart J. 2005 Aug;150(2):288-93.

25. Omran H, Hardung D, Schmidt H, Hammerstingl C, Luderitz B. Mechanical occlusion of the left atrial appendage. J Cardiovasc Electrophysiol. 2003 Sep;14(9 Suppl):S56-S59.

26. Barbato G, Carinci V, Pergolini F, Di Pasquale G. Percutaneous occlusion of the left atrial appendage for systemic embolism prevention in patients with atrial fibrillation: state of the art and report of two cases. Ital Heart J. 2005 May;6(5):409-13.

27. Statistics Canada. Life tables, Canada, provinces and territories, 2000-2002, Table 2b complete life table, Canada, 2000 to 2002: males [Internet]. Ottawa: Statistics Canada; 2006. [cited 2010 Sep 29]. Available from: http://www.statcan.gc.ca/pub/84-537-x/t/pdf/4198612-eng.pdf

28. Johansen HL, Wielgosz AT, Nguyen K, Fry RN. Incidence, comorbidity, case fatality and readmission of hospitalized stroke patients in Canada. Can J Cardiol. 2006 Jan;22(1):65-71.

29. Tu JV, Gong Y. Trends in treatment and outcomes for acute stroke patients in Ontario, 1992-1998. Arch Intern Med. 2003 Feb 10;163(3):293-7.

30. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year survival after first-ever stroke in the perth community stroke study. Stroke. 2003 Aug;34(8):1842-6.

31. Kind P, Hardman G, Macran S. UK population norms for EQ-5D [Internet]. York (UK): Center for Health Economics, University of York; 1999. [cited 2009 Jan 30]. Available from: http://www.york.ac.uk/inst/che/pdf/DP172.pdf

32. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin Scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Making. 2010;30(3):341-54. Epub 2009 Oct 26.

33. Goeree R, Blackhouse G, Petrovic R, Salama S. Cost of stroke in Canada: a one-year prospective study. J Med Econ. 2005;8:147-67.

34. Medical Services Commission payment schedule [Internet]. Victoria: British Columbia Ministry of Health Services; 2010 Apr 1. [cited 2010 Sep 29]. Available from: http://www.health.gov.bc.ca/msp/infoprac/physbilling/payschedule/index.html

35. OCCI costing analysis tool. In: Ontario Case Costing Initiative (OCCI) [Internet]. Toronto: Ontario Case Costing Initiative; 2010 [cited 2010 Jun 22]. Available from: http://www.occp.com/.