Trillium Gift of Life Network

# Addendum

## Ontario Clinical Guidelines

### Ventricular Assist Devices for Destination Therapy

June 16, 2017

# I. Purpose

The Ontario Health Technology Advisory Committee (OHTAC) review of continuous-flow left ventricular devices (LVAD) for destination therapy was published in February 2016. TGLN in partnership with CCN and Ontario's VAD implant centres have produced an addendum to the *Ontario Clinical Guidelines for Ventricular Assist Devices* which address OHTAC's recommendations and provide specific guidelines pertaining to destination therapy.

# II. Summary of HQO Assessment

The objective of Health Quality Ontario's *Left Ventricular Assist Devices for Destination Therapy: A Health Technology Assessment* was to determine the clinical effectiveness of LVADs for destination therapy for patients with end-stage heart failure who are ineligible for heart transplantation and estimate the cost-effectiveness and potential budget impact for the Ontario Ministry of Health and Long-Term Care over the next 5 years. The full report can be found at www.hqontario.ca/evidence, a summary of the 2016 HQO Assessment is provided below.

Clinical Evidence Review

OHTAC examined the quality of evidence regarding key outcomes pertaining to destination therapy. The review was primarily based on four studies, including three systematic reviews and one observational study. It reached the following conclusions:

- Moderate-quality evidence indicates that treatment with continuous-flow LVADs improves survival compared with drugs.
- Moderate-quality evidence indicates that treatment with continuous-flow LVADs had higher adverse event rates than drugs.
- Low-quality evidence suggests that treatment with continuous-flow LVADs improves quality of life compared with drugs.

Economic Evidence Review

OHTAC conducted a search for existing cost-effectiveness and cost-utility analyses of LVADs. Of 519 citations reviewed, 3 studies met the inclusion criteria. Although none took a Canadian perspective, the studies closely aligned with the treatment regimens and comparators in Canada.

The evaluated studies all came to similar conclusions about the potential economic value of LVAD for destination therapy, that LVAD as destination therapy improved survival and quality of life but remained a relatively expensive intervention.

Budget Impact Analysis

OHTAC conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care (MOHLTC). It estimated the number of potential destination-therapy cases to be funded each year based on a ratio of two destination therapy cases to one bridge-to-transplantation case. There having been 47 adult bridge-to-transplantation cases funded by MOHLTC in 2014/15, OHTAC assumed there would be 94 destination-therapy LVADs implanted in the first year, followed by a 20% increase for each subsequent year.

According to OHTAC, the net cost of destination therapy over conventional medical models is $153,150 in the first year, and $44,782 in subsequent years of survival. Based on there being 94 implants, OHTAC estimates the net overall impact to the MOHLTC in year 1 to be approximately $13.6 million. The maintenance cost for the surviving patients and new implant cases in year 5 would be about $45 million.

OHTAC Recommendations

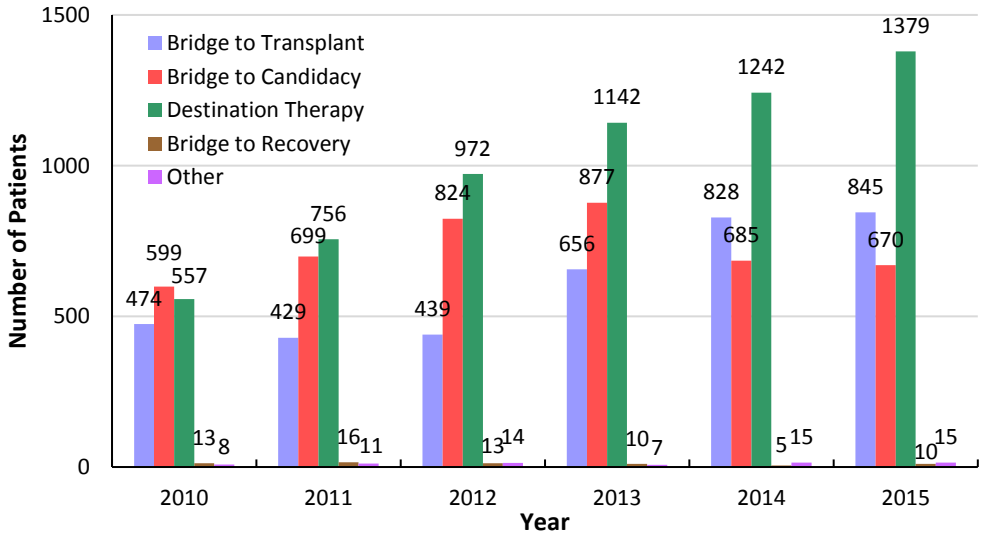
OHTAC concluded that for patients with end-stage heart failure who are ineligible for heart transplantation, permanent treatment with continuous-flow LVADs is effective at improving survival and quality of life compared with drug therapy. The review also found that permanent continuous-flow devices have higher adverse event rates, such as bleeding and infection than drug therapy. Although it improves survival and quality of life, the device itself and the surgery to implant it are very expensive. The Committee's recommendations were as follows:

- OHTAC recommends that continuous-flow left ventricular assist devices (LVAD) be publicly funded as permanent therapy (also known as destination therapy) in patients with end-stage heart failure who are ineligible for heart transplantation.
- OHTAC recommends that the Cardiac Care Network and Trillium Gift of Life Network provide guidance regarding which hospitals should offer this procedure and which patients should be eligible.
- OHTAC further recommends that the Cardiac Care Network and/or Trillium Gift of Life Network ensures data is collected on survival and quality of life for individuals receiving continuous flow LVAD as permanent therapy, and that this data be reviewed by OHTAC in 2 years.

# III. Current Status of VADs for Destination Therapy

Ventricular assist devices can be used to provide circulatory support to assist the damaged left ventricle in patients with end-stage heart failure. Initially developed to provide temporary support while a patient waits for a heart transplantation (bridge-to-transplant), VADs have increasingly been used as an alternative to drug therapy for patients who are ineligible for heart transplantation (destination therapy). Figure 1 provides INTERMACS data for the period 2010 to 2015 showing the progressive increase in VADs implanted for destination therapy. Since 2010, the number of destination therapy implants has increased almost 150%, from 557 to 1379, by 2015 accounting for over 48% of all VAD implants.

Figure 1: Intermac – Implants per Year by Device Strategy Primary Prospective Implants: 2010 to 2015




Source: Data extracted from Intermacs Quarterly Statistical Report 2016 Q1

The growth of destination therapy has likely been enabled by the development of VAD technology. Whereas first-generation VADs used pulsatile pumps to mimic the natural pulsing action of the heart, implanted second-generation VADs use a rapidly spinning rotor to produce a continuous flow into the systematic arterial system. Smaller in size and with fewer moving parts, second-generation VADs require less energy, are more durable and have a reduced risk of infection (Bonacchi et al, 2015).

Although VADs are licensed by Health Canada for both use as bridge to transplant and for patients with end-stage left ventricular failure who have received optimal medical therapy and who are not candidates for cardiac transplantation, their use in Ontario for destination therapy is minimal (Ontario Health Technology Assessment Series, 2016). Table 1 shows VAD volumes at each transplant hospital in Ontario for the last 4 fiscal years, which have increased by about one third over the period.

Table 1: Volumes of Ventricular Assist Devices Implanted at Ontario Hospitals

| | 2012-13 | 2013-14 | 2014-15 | 2015-16 |
|---|---|---|---|---|
| UHN | 20 | 21 | 27 | 34 |
| OHI | 12 | 9 | 15 | 11 |
| LHSC | 3 | 3 | 5 | 6 |
| Sick Kids | 7 | 3 | 5 | 5 |
| **Total** | **42** | **36** | **52** | **56** |

**Source: TGLN**

# IV. Clinical Evidence Background Review

As a relatively new and fast evolving technology, there is a growing body of scientific evidence evaluating the effectiveness of VADs. To ensure the most relevant and up-to-date evidence was consulted, a literature search was performed using PubMed for studies published after 2000 relevant to VADs for destination therapy. Abstracts were reviewed and, for those studies focussing on outcomes and quality of life, full-text articles were obtained. The key points are summarized below.

Survival Rates

Outcomes for patients receiving destination therapy VADs are positive and continue to improve. Among carefully selected patients receiving the latest continuous flow devices, survival rates are comparable to early survival after heart transplant (Kirklin et al., 2015; Ponikowski et al., 2016). The table below provides data from Intermacs comparing annual survival rates by pre-implant device strategy:

Table 2: Percent Survival for Continuous Flow VADs by Pre-Implant Device Strategy: June 2006 to September, 2016

| Years after Device Implant | Bridge to Transplant | Bridge to Candidacy | Destination Therapy |
|---|---|---|---|
| 1 | 84.7 | 82.7 | 76.6 |
| 2 | 76.7 | 72.2 | 64.3 |
| 3 | 66.2 | 61.8 | 53.3 |
| 4 | 54.6 | 51.7 | 44.3 |

Although survival rates for destination therapy are less than for bridge to transplant and bridge to candidacy, this is likely related to the burden of comorbidities that excluded patients from transplantation (Kirklin et al., 2015). Significantly, studies comparing destination therapy patients with those receiving optimal medical management show considerably better survival rates among the former (Bonacchi et al., 2015; Slaughter et al., 2009; Rogers et al., 2007; Rose et al., 2001).

Quality of Life

Patients undergoing a VAD for destination therapy also experience significant improvements in quality of life (Grady et al., 2016; MacIver, Rao, Ross, 2011). VADs are indicated for patients with Stage D heart failure who are at imminent risk of dying either from an acute event or chronic decompensation of existing heart failure. Prior to the advent of mechanical support, patients living with Stage D heart failure who were not eligible for transplant, faced certain death. Symptoms of dyspnea and fatigue worsened over time, functional ability decreased, and psychologic distress increased.

The 2015 ROADMAP study that compared the effectiveness of LVAD patients with optimal medical management patients (OMM) who had ambulatory heart failure found VAD patients have over two times the likelihood of reaching the "primary endpoint based on survival and improvement $\geq$ 75m [6 minute walks] at 12 months" than OMM patients in non-inotrope-dependent heart failure (Estep et al 2015). After

2 years, in addition to meeting their primary endpoint, LVAD patients self-reported much better "mobility, self-care, ability to perform usual activities, pain, and presence of anxiety or depression" than OMM patients (Oddershede, Andreasen, and Ehlers 2014; Starling, et al. 2017). With a VAD, patients can expect the symptoms of heart failure to improve, their functional ability to increase and psychologic distress to decrease. According to one study examining quality of life and functional outcomes at 6 months, patients with destination therapy VADs were able to walk 100m further and had lower New York Heart Association (NYHA) functional class compared with patients in a cardiac resynchronization therapy trial (Rogers, Aaronson, et al 2010). This increased mobility as a result of significantly improved health status and increased cardiac functionality also changes patients' outlook on life as their degree of depression improves after LVAD implantation in comparison with OMM patients (Estep et al 2015).

That patients are no longer confined to hospital for the duration of support, and can participate in everyday activities such as walking and driving has probably contributed the most to improvements in VAD quality of life (MacIver and Ross, 2012). Yet further improvements are required. Power systems are heavy and cumbersome, and with a charge capacity for a pair of batteries of 10 to 12 hours depending on the activity level of the patient, frequent battery exchange is needed for continuous use (MacIver, Rao, Ross, 2011; Thoratec Heartmate II LVAS Instruction for Use, 2015).

Adverse Events

Concerns persist that VADs may predispose patients to an undue burden of adverse events, including post implant bleeding, infection and stroke. Hospital readmission after implantation is frequent and only a small minority of patients are not readmitted for further device management (Hernandez R E, et al., 2015). Recent studies, however, indicate that compared with pulsatile flow devices, continuous-flow VADs are associated with significant reductions in the frequency of adverse events and rates of hospitalization (Slaughter et al., 2009). Furthermore, with the development of third generation devices, which are smaller, simpler in maintenance and less harmful to blood cells, occurrences of adverse events should decline further (Bonacchi et al, 2015; Kirklin et al., 2015; Estep et al., 2015).

# V. Methodology

Following the publication of the OHTAC report, TGLN and CCN met to discuss their response to the recommendations. Both organizations agreed to work with members of the Provincial Heart/Lung Working Group and identified stakeholders to develop an addendum to the *Ontario Clinical Guidelines for VAD*. Although the guidelines apply to all VAD therapies, it was developed at a time when only bridge to transplant insertions were funded and contains limited recommendations on destination therapy. The addendum was developed using the same framework employed for the *Ontario Clinical Guidelines for VAD*.

Review of Existing Guidelines

A review was carried out of relevant recommendations for destination therapy. As well as searching published literature using PubMed, MEDLINE and Cochrane Reports, a jurisdictional scan was performed reviewing VAD guidelines from Canadian and international cardiovascular organizations. The Canadian Cardiovascular Society (CCS) and International Society for Heart and Lung Transplantation (ISHLT) guidelines, from which the *Ontario Clinical Guidelines for VAD* recommendations were predominantly adopted, and the *2016 ESC (European Society of Cardiology) Guidelines for the diagnosis and treatment of acute and chronic heart failure* were found to be the most up-to-date and reputable guidelines containing VAD for destination therapy research and evidence.

Based on this review the following published guidelines were used as reference in the development of the VAD for destination therapy guidelines:

- Ontario Clinical Guidelines: Ventricular Assist Devices
- 2011 CCS Heart Failure Management Guidelines Update: Focus on Sleep Apnea, Renal Dysfunction, Mechanical Circulatory Support, and Palliative Care
- 2013 ISHLT Guidelines for Mechanical Circulatory Support
- ESC: 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure.

A summary of relevant recommendations for destination therapy VADs was completed including:

- All relevant recommendations from the Ontario Clinical Guidelines, the CCS and ESC guidelines;
- All relevant ISHLT recommendations with an evidence level of A (data derived from multiple randomized clinical trials or meta-analyses) or B (Data derived from a single randomized clinical trial or large nonrandomized studies).

ISHLT recommendations with lower evidence levels were also included only if they corresponded to CCS recommendations.

Develop Recommendations on VAD Specific to Destination Therapy

A workshop of key stakeholders from Ontario's heart transplant centres, the CCN, and TGLN took place in October 2016. The main objective was to address OHTAC's recommendations and develop guidelines on VAD specific to destination therapy, especially regarding patient eligibility and institutions that should provide them. To aid guideline development, a summary table outlined the Ontario Clinical Guideline recommendations with the corresponding recommendations from CCS, ISHLT and ESC, and the level of evidence assigned by each organization. The table below describes how each organization assigns their recommendations and evidence levels:

| **Organization** | **Evidence Level** | **Description** |
|---|---|---|
| Canadian Cardiovascular Society | High | Further research very unlikely to change confidence in the estimate of effect |
| | Moderate | Further research likely to have an important impact on confidence in the estimate of effect and may change the estimate |
| | Low | Further research very likely to have an important impact on confidence in the estimate of effect and likely to change the estimate |
| | Very Low | Estimate of effect very uncertain |
| ISHLT/ European Society of Cardiology | A | Data derived from multiple randomized clinical trials or meta analyses |
| | B | Data derived from a single randomized clinical trial or large nonrandomized studies |
| | C | Consensus of opinion of the experts and/or small studies, retrospective studies, registries |

Participants were instructed to review the *Ontario Clinical Guidelines for VADs* and identify whether they were sufficient and applicable to destination therapy. Where recommendations were not sufficient, the group determined whether to adopt recommendations from the published guidelines or develop their own.

Following the workshop, members were given the opportunity to review and provide feedback on the compiled recommendations. To ensure transparency, all feedback was collated, with a summary provided to each participant outlining the action taken on proposed changes to the recommendations. The finalized recommendations were incorporated into an addendum to the *Ontario Clinical Guidelines for VADs* which was reviewed by workshop participants, the Heart/Lung Working Group, and the CCN.

# VI. Destination Therapy VAD Recommendations

## VAD Implant and System Requirements

1. ***Destination Therapy Volumes***
   Currently, VAD programs do not have the capacity to implant the OHTAC estimate of 2 destination therapy VADs for every bridge-to-transplant VAD. Ontario programs estimate that in total, 35 destination therapy VADs will be implanted in the first year across the province. This estimate considers existing system capacities, resources, and experience required to ensure patient quality of care.

   Over the next five years, destination therapy volumes are expected to increase as VAD programs expand, gain more experience, and patient outcome data become available. It is expected that over the next five to ten years, destination therapy volumes will increase to OHTAC's 2 destination therapy for every 1 bridge to transplant estimate.

2. ***Institutions Providing Destination Therapy***
   Due to the level of surgical and medical expertise required, VADs for destination therapy should currently only be implanted at heart transplant centres in Ontario. After implant, implanting centres will continue to assume care of patients but will work towards a shared care model with community hospitals to provide follow-up care closer to home.

   Non-transplant centres wishing to launch a VAD program must, as with transplant centres, demonstrate medical and surgical certification in mechanical circulatory support as evidenced by ABIM or Royal College Certification in Advanced Heart Failure, or STS certification in Mechanical Circulatory Support (MCS).

3. ***System Monitoring and Performance Measurement***
   VAD volumes should be monitored to ensure that transplant centres across Ontario have access to the funding required to perform the treatment therapies. Centres should report VAD volumes and performance indicators on a quarterly basis.

   Performance indicator data should be collected prior to implant, during hospital admission, and post-implant, at pre-determined intervals. Indicators should include, but not be limited to, patient outcomes such as survival, adverse events, hospital readmissions, and quality of life measures.

## Patient Indications

4. ***Permanent mechanical circulatory support (MCS) should be considered for highly selected transplant ineligible patients with the capacity for meaningful recovery of end-organ function and quality of life, who fulfill the following criteria:***

   a. Patients whose ventricular function is deemed unrecoverable or unlikely to recover without long-term device support,

   b. Patients who have required hospitalization for decompensated heart failure with inotropic support OR are intolerant of goal-directed therapies for 45 of the previous 60 days (ACEi and beta-blocker) with exercise testing demonstrating a pVO2 of $\leq$ 14 mL/kg/min (if able to perform).

## Patient Evaluation

***5. Assessment of VAD Care and Independent Living***

Patients must undergo formal assessment of their ability to take care of their VAD and live independently as an outpatient. This includes assessment of a patient's activities of daily life (ADL) and psychosocial support. Where applicable, patients may also receive psychosocial, neurological and cognitive testing.

***6. End of Life Planning***

Health care providers must have a documented discussion with patients on goals of care before implantation.

***7. Absolute Contraindications***

The following are conditions relating to destination therapy VAD candidates that constitute absolute contraindications to implant.

a. **Untreatable end-organ disease:** Patients with chronic diseases whose quality of life will not be improved by VAD therapy.

b. **Pulmonary Hypertension:** Patients with pre-capillary pulmonary hypertension and lack of adequate response to treatment with pulmonary vasodilators or significant right ventricular dysfunction.

c. **Primary lung disease:** Patients with chronic vent dependent or progressive oxygen dependent primary lung disease.

d. **Malignancy:** Patients with an expected survival of less than 3 years.

***8. Relative Contraindications***

The following are conditions relating to destination therapy VAD candidates that constitute relative contraindications to implant.

a. **Kidney disease:** Patients who require chronic dialysis.

b. **Liver Disease**: Patients with severe fibrosis.

c. **Bleeding:** Patients with chronic gastrointestinal bleeding (GI) such as colitis or varicies, or any contraindication to chronic anticoagulation.

d. **Peripheral vascular disease:** Patients with severe peripheral vascular disease.

e. **Non-Dilated Cardiomyopathy –** Patients with small LV cavity (e.g. non-compaction or restrictive processes)

f. **Neurological disorder:** Patients with neurological disorders severe enough to affect basic activities of daily life and VAD care.

g. **Cognitive disorder:** Patients with history of cognitive dysfunction severe enough to affect basic activities of daily life and VAD care.

h. **Psychosocial considerations:** Patients with psychosocial conditions that may limit their ability for VAD care, including;
   i. High risk/destructive addictive behaviour
   ii. Psychiatric conditions leading to concerns over VAD care

i. **Social Support:** There must be a reasonable expectation for the patient to be discharged from the acute care setting and live independently as an outpatient.

## Patient Management

***9. ICD Placement***

Routine placement of an ICD may be considered for patients who did not have an ICD prior to VAD implant.

***10. Destination Therapy Replacement***

Patients must continue to meet criteria for destination therapy if a subsequent VAD is required.

# VII. References

Bonacchi M, Harmelin G, Bugetti M, Sani G. "Mechanical Ventricular Assistance as Destination Therapy for End-Stage Heart Failure: Has it Become a First Line Therapy?" *Frontiers in Surgery* 2015 Vol 1

Estep J, Starling R, Horstmanshof D. "Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients" *Journal of the American College of Cardiology* 2015 Vol 66, No. 16

Feldman D, Pamboukian SV, Teuteberg J J, et al. "The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support" *The Journal of Heart and Lung Transplantation* 2013 Vol 32, No.2

Grady K, Naftel D, Myers S, et al. "Change in health-related quality of life from before to after destination therapy mechanical circulatory support is simila for older and younger patients: analyses from INTERMAC" *The Journal of Heart and Lung Transplantation* 2015 Vol 34, No. 2

Hernandez RE, Singh SK, Hoang DL, et al. "Present-Day Hospital Readmission after Left Ventricular Assist Device Implnatation: A Large Single-Center Study" *Tex Heart Inst J.* 2015 Vol 42, No. 5

Intermacs *Quarterly Statistical Report 2016 Q1* *https://www.uab.edu/medicine/intermacs/*

Katz MR, Dickinson MG, Nirav Y, et al. "Outcomes of Patients Implanted With a Left Ventricular Assist Device at Nontransplant Mechanical Circulatory Support Centers" *American Journal of Cardiology* 2015 Vol 115, No. 9

Kirklin J, Naftel D, Pagani F, Kormos R, Stevenson L. "Seventh INTERMACS annual report: 15,000 patients and counting" *The Journal of Heart and Lung Transplantation* 2015 Vol 34, No. 12

MacIver J and Ross H "Quality of Life and Left Ventricular Assist Device Support" *Circulation* 2012 Vol 126, No. 7

MacIver J, Rao V, Ross H "Quality of life for patients supported on a left ventricular assist device" *Expert Review of Medical Devices* 2011 Vol 8, No. 3

McKelvie RS, Moe, GW, Cheung A, Costigan J, Ducharme A, et al. "2011 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Sleep Apnea, Renal Dysfunction, Mechancial Circulatory Support, and Palliative Care" *Canadian Jounral of* Cardiology 2011 Vol 27

Oddershede, L., Andreasen, J.J., and Ehlers, L. "Estimation of utility values from visual analog scale measures in patients undergoing cardiac surgery." *Clinicoecon Outocmes Res.* 2014 Vol 6.

Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, et al. "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure" *European Heart Journal* 2016 Vol 37

Rogers JG, Aaronson KD, Boyle AH, et al. "Continuous Flow Left Ventricular Assist Device Functional Capacity and Quality of Life of Advanced Heart Failure Patients" *Journal of American College of Cardiology* 2010 Vol 55, No. 17

Rogers JG, Butler J, Lansman SL, Gass A, Portner PM, Pasque MK, et al. "Chronic Mechanical Circulatory Support for Inotrope-Dependent Heart Failure Patients Who Are Not Transplant Candidates: Results of the INTrEPID Trial." *Journal of the American College of Cardiology* 2007 Vol 50, No. 8

Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. "Long-term use of a left ventricular assist device for end-stage heart failure." *N Engl J Med* 2001 Vol 345, No. 20

Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte J V, Feldman D, et al. "Advanced heart failure treated with continuous-flow left ventricular assist device" *N Engl J Med* 2009 Vol 361, No. 23

Starling RC "Risk Assessment and Compartive Effectiveness of Left Ventricular assist Device and Medical Management in Ambulatory Heart Failure Patients: The ROADMAP Study 2-Year Results." *JACC: Heart Failure* 2017

Stewart GC and Givertz MM "Mechanical Circulatory Support for Advanced Heart Failure" *Circulation* 2012 Vol 125, No. 10

Stewart GC, Miller LW and Stevenson LW "Keeping Left Ventricular Assist Device Acceleration on Track" *Circulation* 2011 Vol 123, No. 14