



## Common Drug Review *Patient Group Input Submissions*

### **Ivabradine (Lancora) for Heart failure, NYHA class II to IV**

**Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.**

Heart Failure Support Group of Manitoba — permission granted to post.

The HeartLife Foundation — permission granted to post.

#### **CADTH received patient group input for this review on or before November 29, 2016**

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter. This includes patient input received from individual patients and caregivers as part of that pilot project.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

## Heart Failure Support Group of Manitoba

### Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Ivabradine
Name of the patient group	Heart Failure Support Group of Manitoba
Name of the primary contact for this submission:	[REDACTED]
Position or title with patient group	Member- main contact person for the support group
Email	[REDACTED]
Telephone number(s)	[REDACTED]
Name of author (if different)	
Patient group's contact information: Email	[REDACTED]
Telephone	204-256-9878
Address	[REDACTED] Winnipeg, Manitoba,
Website	none
Permission is granted to post this submission	Yes

#### 1.1 Submitting Organization

The Heart Failure Support Group of Manitoba (HFSG) was established in 2011. Membership composed of patients with diagnosis of heart failure and their family members/ caregivers.

The purpose of the group is to provide support, education and the opportunity for heart failure clients and their families / caregivers to interact with others with similar situations. Members meet formally on a quarterly basis but also meet informally. The group activities include education sessions where speakers are invited on topics that are relevant to care of those with heart failure or relevant to caregivers, invited guests/ speakers to talk on topics relevant to members including current management for heart failure. There are also social networking and gathering.

#### 1.2 Conflict of Interest Declarations

a) *We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:*

The Heart Failure Support group have received financial support from Servier

b) *We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:*

Estrellita Estrella-Holder, RN, the co-founder of this group and our support member from the Heart Failure Clinic, has received honorariums from Novartis and Servier.

## **Section 2 — Condition and Current Therapy Information**

### **2.1 Information Gathering**

Information about the various treatments in heart failure including Ivabradine was discussed in various education sessions provided to the group in September 2016 as well as during the annual public awareness on management of heart failure education session over the last 3 years conducted by the Heart Failure Clinic at St. Boniface Hospital. We understand that this medication has been included the Canadian Cardiovascular Society recommendation for the management of heart Failure in 2014 ( conditional recommendation awaiting approval by Health Canada).

### **2.2 Impact of Condition on Patients**

Patients with heart failure suffer from various symptoms including breathlessness, fatigue, reduced appetite, reduced activity tolerance, difficulty sleeping at night due to breathing problems, sometimes confusion and impaired memory to name a few. There are many activities in daily living that many of us are unable to do due to heart failure symptoms. The heart failure symptoms impair the quality of our lives. It is important for us to be able to control our symptoms of heart failure to help improve the quality of our lives and of our families.

### **2.3 Patients' Experiences With Current Therapy**

The guideline for treatment of heart failure includes the use of Ace-inhibitor or Angiotensin receptor blockade, beta blockers, and mineralocorticoid receptor antagonist (triple therapy). In spite of advances in the treatment of heart failure, 5-year mortality remains at 50%. Some patients do not tolerate some of these medications. Side effects include, but not limited to, lowering of blood pressure, fatigue or tiredness, increased potassium, and many others. Some patients because of co morbidity, are unable to take beta blockers. It is our understanding that there is a group of patients with heart failure who may benefit from the addition of Ivabradine, a heart rate slowing medication. This includes patients who could not tolerate beta blockers such as those who suffer from increasing fatigue on beta blockers, those with co morbidity such as those with asthma or reactive airway problems, those who have borderline blood pressure. The usual triple therapy is accessible.

We know that with each heart failure exacerbation, there is progressive loss in functional capacity and we rely very much with our family care providers as well as community support services (home care). Some of us may eventually require a change in living situation such as moving to a supportive housing especially those who do not have enough social support.

### **2.4 Impact on Caregivers**

As heart failure progress and as we become more symptomatic, we become more reliant to our family care providers. Progression of illness means potential loss of income for family members as well who may have to miss work to help us with our activities of daily living. Our caregivers suffer emotionally as well with us. As we require more help, care givers take care of themselves less and less.

Caregiving could be a rewarding experience but it can also be extremely demanding and can cause stress. The caregiving process could have negative effect on caregiver's overall health and well-being. Many factors in caregiving could lead to stress including the level of care needed, physical strain, financial hardship as managing heart failure is quite costly, emotional factors and lack of support from others. The longer a caregiver provides caregiving activities, the more likely that the caregiver's physical and emotional health will worsen.

## Section 3 — Information about the Drug Being Reviewed

### 3.1 Information Gathering

Information about the various treatments in heart failure including Ivabradine was discussed in various education sessions provided to the group in September 2016 as well as during the annual public awareness on management of heart failure education session over the last 3 years. One on one discussion with some patients in relation to possible use of this drug if and when it becomes available.

### 3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

#### a) *Based on no experience using the drug:*

Major advances in treatment of heart failure are being made including the use of Ivabradine, a heart rate slowing medication. The SHIFT trial significantly improved the outcomes of those treated with Ivabradine compared to the usual treatment of heart failure. It showed reduction in death by 18 %, as well, patients who were in the Ivabradine treatment group had less hospitalization compared to the other group treated the usual way. Reducing hospitalization to us means less symptoms and improvement in the quality, not only of our lives but our families'. This treatment as we know is available in many countries for several years now and yet remains unapproved in Canada. We understand that it will not be indicated for all heart failure patients but there is a group of heart failure patients who could benefit from its use. It could be one of us. Reduce hospitalization and improvement in symptoms could translate into less financial constraints due to less time off work by patients and care providers. Reduce hospitalizations and readmission could be potentially cost savings for our health care.

#### b) *Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:*

AS above, the SHIFT trial significantly improved the outcomes of those treated in the Ivabradine group as compared to the control group (those who did not receive Ivabradine). Reduction in hospitalization translate into control of heart failure symptoms or vice versa. Ivabradine causes

## Section 4 — Additional Information

Heart Failure affects over 600,000 Canadians and it is a rising epidemic. It is the leading cause of hospitalizations and readmissions which is costing our country millions of dollars in health care spending. We suffer poor quality of life from this condition. Our families suffer with us. We would like to be able to be given equal access to life prolonging drugs that are already widely used in other countries through expedient or accelerated evaluation and approval process of life prolonging and symptoms relieving medications for heart failure including the medication Ivabradine. It would be helpful as well to make the feedback process simple for any individual who may want to provide feedback through this process.

## The HeartLife Foundation

### Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Corlovan (Heart Failure)
Name of the patient group	The HeartLife Foundation
Name of the primary contact for this submission:	[REDACTED]
Position or title with patient group	[REDACTED]
Email	[REDACTED]
Telephone number(s)	[REDACTED]
Name of author (if different)	[REDACTED]
Patient group's contact information: Email	[REDACTED]
Telephone	604-679-5810
Address	[REDACTED] Vancouver, BC, [REDACTED]
Website	<a href="http://www.heartlife.ca">www.heartlife.ca</a>
Permission is granted to post this submission	Yes

#### 1.1 Submitting Organization

**Context.** An estimated 600,000 people are currently living with heart failure in Canada (Heart & Stroke Foundation, 2016). In their 2016 Report on the health of Canadians, the Heart & Stroke Foundation estimates that 50,000 Canadians are diagnosed with heart failure each year and this number is on the rise. Heart failure costs the Canadian healthcare system more than \$2.8 Billion dollars per year – with the majority of those dollars being spent on acute care. Research has shown that effective patient engagement improves clinical outcomes, prevents hospitalizations, increased patient self-efficacy for managing their condition, and overall quality of life. Despite these findings, few organizations currently exist to help heart failure patients self-manage their condition, provide education and support for patients and families, and advocate for access to care and innovative treatments. The HeartLife Foundation was created in response to this need.

**Organization History.** Founded in June 2016 by Dr. Jillianne Code, a heart transplant recipient, and Mr. Marc Bains, a heart failure survivor, HeartLife aims to drive healthcare innovation and transformation by adding patient voices to the heart failure conversation. In collaboration with Dr. Sean Virani, one of Canada's leading heart failure specialists and promoter of patient and family centred care, we endeavour to ensure that there is an open dialogue including patients as partners with healthcare providers, government, and industry across Canada. Our members are all patients along the heart failure continuum, their families and care givers.

**Vision.** HeartLife is the patient voice for heart failure in Canada.

**Mission.** We aim to empower patient voices to stimulate dialogue, advance understanding, improve access to treatments and research, raise heart failure awareness, and improve patient care in Canada.

### **Principals:**

#### **Jillianne Code, Ph.D**

Co-Founder & President, Board Member

Dr. Jillianne Code is a 2-year heart transplant recipient and 9-year heart failure survivor, assistant professor at University of Victoria, post-doctoral fellow at Harvard University, keynote speaker, blogger at [heartfailuretoharvard.com](http://heartfailuretoharvard.com), and passionate advocate for patient and family centred care.

#### **Marc Bains, BBA**

Co-Founder & Vice President, Board Member

Mr. Marc Bains has been living with heart failure for more than 9 years, holds a BBA in Entrepreneurial Leadership from Kwantlen Polytechnic University, an independent financial advisor and marketing consultant for start-ups, is passionate about promoting a coordinated approach to heart failure care in Canada.

#### **Sean Virani, MD, MSc, MPH, FRCPC**

Medical Director, Board Member

Dr. Sean Virani is a cardiologist and key opinion leader for heart failure in Canada, associate professor of medicine at University of British Columbia, President of the Canadian Heart Failure Society, provincial leader and advisor for heart failure, and is a passionate advocate for heart failure patients and healthcare transformation.

### **1.2 Conflict of Interest Declarations**

The HeartLife Foundation has received an Educational Grant from Servier Canada, honoraria for presenting at the Canadian Cardiovascular Congress 2016 in Montreal from Servier Canada and the Canadian Cardiovascular Society, and a Project Grant from Novartis Canada.

None of the aforementioned organizations played any role in this submission.

## **Section 2 — Condition and Current Therapy Information**

### **2.1 Information Gathering**

Information obtained to complete Condition and Current Therapy Information was obtained primarily through the lived experiences of Jillianne Code and Marc Bains, one-on-one conversations with medical experts, health care professionals, other patients with heart failure, family members and caregivers.

### **2.2 Impact of Condition on Patients**

Heart failure is a condition that requires continuous daily monitoring, adherence, and vigilance on the part of the patient in order to control the delicate balance of symptoms. These symptoms include: shortness of breath, extreme fatigue, low blood pressure, dizziness, edema and bloating. Many patients also have palpitations and arrhythmia as a result of the underlying etiology of the cause of their heart failure. Depending upon the stage and severity of the disease, the effect of the symptoms can vary. To illustrate, we provide the following example lived experiences based on our personal narratives and on the information gathered as indicated in Section 2.1. Prior to these narratives, however, HeartLife offers this information with the following caveat. Much of the focus on current heart failure care in Canada, and internationally, is primarily on medical and surgical interventions – interventions that are of course critical in advancing the treatment and survivability of patients like us, but for the patient and family members living with heart failure this is only one part of the whole picture of this disease. We hope that with the information provided below, the committee will obtain a better overall idea of what it's like to

live day to day with this disease as it progresses. Note, that there is no cure for heart failure and treatments serve only to manage symptoms and prolong survivability heart transplantation, if the patient is eligible.

### **Depression and Anxiety**

With an initial diagnosis of heart failure, most patients quickly develop high levels of anxiety, coupled with bouts of depression, anger, and grief as one comes to terms with the diagnosis and the immediate impact it has on their life. There is increasing evidence that heart failure patients, especially after initial diagnosis and through later stages of the disease, develop symptoms of Post-Traumatic Stress Disorder that can potentially exacerbate the disease (e.g. Spitzer et al., 2009; Tulloch, Greenman & Tasse, 2015). Medical teams often place a lot of emphasis on ‘restricting’ aspects of a patients’ life – or at least that is how it often feels. Fluid restriction. Sodium restriction. Alcohol restriction. Caffeine restriction. Food restrictions. For the vast majority of patients, these restrictions are often overwhelming leading patients into prolonged states of depression and anxiety in addition to adding to the physical manifestations of the disease which often prevent them from doing the activities they were normally doing prior to their diagnosis. These include working a regular job, travelling, sports, and other outdoor activities, participating in family events. Access to psychiatry and psychological counselling is often sporadic, depending almost entirely upon private or employer insurance coverage. If the patient is one of the 15% of the current 600,000 estimated heart failure patients in Canada who are fortunate enough (or critical enough) to have access to specialized heart function clinics, these clinics often offer integrated counseling and psychiatric services. However, the vast majority of patients – more than 85% – do not have this kind of holistic care leaving them to suffer alone in silence, leaning heavily on their unqualified primary physician (if they have one) to coordinate care, spouses, family and caregivers for support.

### **NYHA Class I or II**

While in NYHA Class I or II, symptoms could be mild to moderate most days which means that laying down to sleep requires one or two pillows to help you be able to breathe at night while sleeping. Sleep is often restless, and disturbed, but if congestion is controlled well with medication, fluid restriction, and a low sodium diet, resting is possible. A daily nap is not unusual in these stages. In terms of daily activity, with mild to moderate symptoms, doing basic house hold chores and working in a non-strenuous job is manageable – as long as the patient is careful to adhere to the daily regimen of medications, diet, fluid restriction, and ensure that they get the rest they need. Weekends are often spent napping and resting. With exposure to others in the workplace, many heart failure patients are quick to catch seasonal colds and flus, which can easily exacerbate and even worsen heart failure symptoms potentially leading to hospitalization. In addition, with any physical activity, patients in this class will often have to take frequent breaks, will tire easily, become short of breath on exertion, and have to be careful to avoid extreme weather conditions (hot/cold). Many patients find regular exercise challenging, and demoralizing, and often walking on flat surfaces for short distances is all they can manage. Symptoms change daily.

### **NYHA Class III**

Patients in NYHA Class III, are at higher and – if they can tolerate it – the most ‘optimal’ or recommended dosages of current medications including. Because symptoms are more difficult to control because of the increasing weakening or damage to the heart muscle as a result of the underlying disease causing the heart failure, patients are even more limited. Breathing at night is often congested, leaving patients with an increase in their diuretics thus increasing the frequency urination, leading to even more interrupted, and often sleepless nights. If a patient can sleep, it is often with at least two pillows. Standard treatment also dictates an increase in beta-blockers which artificially slow the heart

rate of patients, leading to further feeling of fatigue, resulting in an increased likelihood of depressive episodes. Many patients have trouble tolerating beta blockers and are often not on the optimal dosage because of this intolerance – placing them at an increased risk of poor outcomes. Patients in this class are often fitted with an Internal Cardioverter Defibrillator (sometimes with a pacemaker) and have an ejection fraction (EF) of less than 30%, have low blood pressure (as a result of the combination of medication and as a function of the disease). To illustrate Marc Bains shares a story of his lived experience below.

**Marc Bains.** *I have been living with Heart Failure for 8 years. I was in disbelief when I received my initial diagnosis. I was 23, fit, and immersed in an exciting career. At the time, I had no indication of what Heart Failure was and how it would drastically affect my life. From 2008 – Present, my EF has been between 10%-25%. My most recent exam indicates 18%. My blood pressure is on average 90/65. Personally, it was most important for me to get back to a “normal” life. Well, as normal as can be, living with heart failure. It was important for me to effectively manage my EF/HR/BP and get back into the routine of work, exercise, and daily activities. The current state of my health has not come without hurdles. The condition has and continues to affect my day-to-day life. At present time, I am unable to work full-time, exercise regularly, travel to remote areas, and take part in many daily activities I once enjoyed (hiking, playing squash, skiing). Furthermore, there have been 3 incidents when the condition has prevented me from driving for a period of 6 months each. During these periods my activities included resting, resting, walking, and resting. Not the life I imagined at 23.*

### **NYHA Class IV**

Patients in NYHA Class IV are in end-stage heart failure. Essentially this means, that despite optimal medical therapy, maximum dosages of medications, the only remaining alternatives for treatment are high risk high cost surgical interventions including: Mechanical support including left ventricular assist devices (LVAD), and heart transplantation. Patients in NYHA Class IV are very sick. Medical therapies are failing as their heart muscle has deteriorated to the point that severe edema in the legs and abdomen, and congestion in the chest lead to many sleepless nights, often sitting up in a chair to rest. Breathing in a horizontal position feels more like choking, gasping for air. Many have described it as feeling like you are drowning. Daily activities are difficult and exhausting, leaving most patients to spend the majority of their time resting at home, living increasingly isolated lives. Cognitive impairments become more severe as a result of the lack of blood flow to the brain resulting in difficulty focusing, reading, carrying on conversations. Most severe patients are often assessed for their suitability for listing for a heart transplant at this stage, end of life discussions are had, and a left ventricular assist device is often placed as a bridge to transplantation. To illustrate Jillianne Code shares a story of her lived experience below.

**Jillianne Code.** *It is difficult to try and I tell all the details of my story. I could discuss about how for most of my adult life I have suffered, how at 28 heart failure literally squeezed the life out of my body, how I struggled to breathe with what felt like a vice around my chest. That despite a stroke, multiple ICD shocks, a left ventricular assist device, severe GI bleeding, countless transfusions, 13 months on the transplant list, a heart transplant, 8 days in a coma with multi organ failure, delirium, and having to learn to feed myself and walk again – that I refused to die. In the world of chronic illness, people often speak of finding your ‘new normal’. Those who are in it now, will understand what I mean. But even if you have never been there I think you can probably imagine what it might be like to have something so profound happen to you that you need to readjust your horizon. Constantly needing to find a ‘new normal’. 2 years after my transplant, two and a 1/2 years after my LVAD, 10 years after my diagnosis I still wonder at the logic of this statement. What does that even mean? What is normal, anyway?*

### 2.3 Patients' Experiences With Current Therapy

As long as patients have access to qualified care providers with an understanding of the latest developments in heart failure treatments, most often identified by the Canadian Heart Failure Society guidelines adopted across the country, then placing patients on optimal therapy is a matter of following the guidelines.

Current treatments include the 'Triple Therapy' of ACE-Inhibitors (or ARBs if ACE-I are intolerant), Beta Blockers, and MRAs. The efficacy of this triple therapy has been well established and extremely successful in managing patients' conditions with respect to reducing mortality and hospitalizations. Both Marc Bains currently benefits from this triple therapy, and Jillianne Code prior to her transplant was on this optimal therapy. However, based on the research conducted to-date, the Canadian Heart Failure Society has identified, and aligned, the Canadian Heart Failure guidelines to include ivabradine should it become available in Canada as it has shown considerable success in European countries and is integrated in the European Cardiology Society Heart Failure Guidelines for some time. Where the efficacy of current treatments are good, many patients remain intolerant to Beta Blockers and in some cases to ACE-Inhibitors, so there is a significant need to have medications to add to these patient's regimen or to even switch them to.

**Marc Bains.** *I am currently managing my condition with a medication plan, a healthy diet low in sodium, and exercise. Although I am "well" by heart failure standards, there is much work to do. I am currently on beta-blockers, Lasix, anti-coagulants, and blood thinners. Combined, these therapies have allowed me to continue living. Living a stable life. Personally, I prefer progress and not stability. I believe that ground breaking therapies that can improve patients' lives and decrease mortality should be readily accessible. It frustrates me as a patient to know that a specific therapy that is not available can and will increase my quality of life.*

### 2.4 Impact on Caregivers

The challenges of heart failure on caregivers and family members cannot be understated. There is a significant burden as the disease is most prevalent in elderly patients who have a number of co-morbidities and are already challenging to medically manage. Not to mention, for those patients who are younger and are affected by this disease, their partners and family members also have to make drastic life changes and sacrifices to meet the demanding needs of this devastating illness. As a patient progresses through each stage of the disease, the physical and psychological trauma is felt by the patient with heart failure but equally so by the spouse or care giver. Marc Bains gives a lived experience account of what I has been like for his wife and family below.

**Marc Bains.** *Many of the challenges faced by patients are similar to those of caregivers. In many cases, the condition affects caregivers physically and mentally. My wife, family and friends are aware of my condition and are in turn 'alert' when with me. Living with someone that has heart failure impacts household diet, routines, and travel. It is not uncommon for my wife to think that I am going to pass out if I feel light headed. She knows, that a cardiac arrest can happen and any time. For that reason, she drives when we go out, she sacrifices travel aspirations, and feels bad when I can enjoy the same activities she does. Almost everyone around me has taken CPR training. One time, two of my closes friends had to give me CPR for 8 minutes, until paramedics arrived. This disease has affected everyone I know and love.*

## Section 3 — Information about the Drug Being Reviewed

### 3.1 Information Gathering

Information obtained to complete Information about the Drug Being Reviewed was obtained primarily through the lived experiences of Jillianne Code and Marc Bains, one-on-one conversations with medical experts, health care professionals, other patients with heart failure, family members and caregivers.

### 3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

**It is expected that the lives of patients will be improved by this new drug – Especially quality of life**

For the population of patients that ivabradine (Corlovan) is expected to benefit, although some studies report that the effects of ivabradine are neutral in populations with CVD and angina in regards to all-cause mortality, there are significant effects on patient-reported outcomes of Quality of Life (Norris & Baney, 2016). As Norris and Baney states, there is an impressive body of evidence demonstrating that patient involvement leads to increased knowledge about treatment options, more realistic expectations regarding disease course and treatment, improved adherence to therapy, and enhanced patient satisfaction (2016).

**There a particular gap or unmet patient need in current therapy that this drug will help alleviate.**

A significant number of patients have a difficult time tolerating increased dosages of beta-blockers with large number of patients who never reach optimal dose as recommended by the Canadian Heart Failure Society guidelines (2015). In regards to tolerance, patients often report dizziness, postural hypotension, and hypoglycemia if a patient also has diabetes – a common heart failure comorbidity. As a result, there is significant need to treat these patients with additive and/or alternative medications and ivabradine (Corlovan) has been shown to be an effective treatment as evidenced by the plethora of literature available.

**Marc Bains.** *It is expected that the lives of patients' (and my life) will be improved with this specific therapy. I am currently on the maximum dosage for all medications including ACE inhibitors and beta blockers. My ability to improve my condition is minimal without an add-on therapy such as Corlovan. I would be willing, to an extent, to experience adverse effects if my Quality of Life improved and my overall mortality rate decreased. As this is a new drug for Canada there aren't any current Canadian patients on this medication.*

## Section 4 — Additional Information

Generally speaking the questions were clearly stated and the examples provided helped to focus on the types of information that would be most useful to the committee during review. As patient,s we already play a vital role in the life the span of a drug. From initial need, to development and research and finally market approval. The patient should always have input as it is their lives that are most effected. We would like to suggest that there be additional inclusion of Patient Voices from the beginning stages of the approval process similar to the pan-Canadian Oncology Drug Review.

Thank you for the opportunity to provide input into this process.

**References:**

Norris, C. & Baine, K. (2016) Does Ivabradine SIGNIFY Improvements in Quality of Life? *Circulation: Cardiovascular Quality and Outcomes*, 9(1): 5-6.

Heart & Stroke Foundation. (2016). *2016 Heart and Stroke Foundation Report on the Health of Canadians*. Ottawa, ON.

Tulloch, H., Greenman, P., & Tasse, H. (2015). Post-traumatic stress disorder among cardiac patients: Prevalence, risk factors, and considerations for assessment and treatment. *Behavioral Sciences*, 5(1): 27-40. DOI: 10.3390/bs5010027

Spitzer, C., Barnow, S., Völzke, H., John, U., Freyberger, H. & Grabe, H. (2009). Trauma, posttraumatic stress disorder, and physical illness: Findings from the general population. *Psychosomatic medicine*. 71(9): 1012-1017. DOI: 10.1097/PSY.0b013e3181bc76b5.