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For information on content, please contact:
Nicole Parent, RN, MSc, PhD, and
Paula Price, RN, PhD, Co-Editors
Canadian Council of Cardiovascular Nurses
202 – 300 March Road,
Ottawa, Ontario K2K 2E2
Phone: 613-599-9210, Fax: 613-595-1155
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Did you know?

Why Amiodarone Requires Diligent Monitoring?

Dorothy Morris, RN, MA, CCN(C), and Nancy Cameron, RN, BScN, CCN(C)

Common clinical questions and practice considerations

1. One of the potential side effects of amiodarone is a prolonged QTc interval that could result in a pro-arrhythmic effect. What is considered a prolonged QTc?

Men > 0.44 secs or 440 ms
Women > 0.46 secs or 460 ms

2. Are there situations that increase the risk of "Torsades de Pointes" (TdP) type of ventricular tachycardia when administering amiodarone?

Two or more of the important risk factors (examples listed below) would need to be present for the potential of TdP to occur (Vancouver Island Health Authority, 2006; Woosley, 2011).

Important risk factors

Baseline ECG abnormalities:
- Marked bradcardia
- Abnormal T waves (e.g., >5mm in height in limb leads or >10mm high in precordial leads, tall and pointed or opposite polarity of the QRS)
- Prolonged QTc

Cardiac medications:
- Sotalol
- Quinidine

Non-cardiac medications:
- Antihistamines
- Antibiotics (e.g., erythromycin, clarithromycin)
- Antifungals (e.g., fluconazole)
- Antipsychotics (e.g., haloperidol, loxapine)
- Anti-depressants (e.g., selective serotonin reuptake inhibitors such as celexa or paxil, selective norepinephrine reuptake inhibitors such as effexor or cymbalta, or tricyclics, such as elavil or imiprex)
- Antiepileptics (e.g., phenytoin, carbamazapine)

Others:
- Female gender
- Structural heart disease
- Advanced age

3. What are some of the unique properties of amiodarone and why do cardiologists sometimes continue the drug in the presence of a prolonged QTc interval?

Amiodarone is a unique iodine-containing, lipophilic, highly protein bound, antiarrhythmic medication that has effects on each of the antiarrhythmic drug classifications (Cahoon, Flattery, & Hess, 2007; Cheng, 2010; Palatnik, 2008; Roberts, 2010; Siddoway, 2003). It interferes with multiple ion channels of myocardial conduction, acting like a sodium blocker (class I), a beta blocker (class II), a potassium channel blocker (class III) and a calcium channel blocker (class IV) (Palatnik, 2008; Roberts, 2010). Since the majority of the drug's action is on the blocking of potassium channels, amiodarone is categorized as a class III antiarrhythmic agent (Cheng, 2010; Palatnik, 2008; Siddoway, 2003). With potassium blocking action you should monitor for a prolongation of the QTc interval with the potential for TdP type of ventricular tachycardia developing, especially if amiodarone is used concomitantly with other drugs, or clinical conditions that prolong a QTc such as marked bradycardia or electrolyte abnormalities (Cahoon et al., 2007; Roberts 2010; Vancouver Island Health Authority, 2006). While you should always monitor the QTc interval when administering amiodarone, the other antiarrhythmic properties of sodium, calcium and beta blocking usually prevent TdP from occurring (Goldschlager et al., 2007; Siddoway, 2003; Vancouver Island Health Authority, 2006). Even when the QTc is 500 ms, the risk of amiodarone induced ventricular tachycardia is extremely rare (Goldschlager et al., 2007; Roberts, 2010; Siddoway, 2003; Vancouver Island Health Authority, 2006). In evaluating the risks versus the benefits of continuing the medication, cardiologists will sometimes lower the dose and correct other clinical conditions impacting the QTc.

When given intraveneously (IV), amiodarone's initial effects relate to beta-blockade with lesser effects on the other antiarrhythmic properties of sodium, calcium and potassium blockade (Vancouver Island Health Authority, 2006). Amiodarone IV is considered a vesicant and,

therefore, requires a 0.22 micron filter whether given as an intermittent or continuous infusion (Vancouver Island Health Authority, 2010). Filtering of the medication may be delayed in emergent cardiac arrest situations when direct IV dosing is required. IV administration requires the patient to be on an ECG monitor, with frequent blood pressure monitoring for hypotension (Cahoon et al., 2007; Vancouver Island Health Authority, 2010).

When given orally, amiodarone has more effects on blocking calcium, sodium, and in particular, potassium (Cahoon et al., 2007; Vancouver Island Health Authority, 2006). It can take three to six weeks to get the full antiarrhythmic effects of amiodarone, as the drug accumulates in adipose tissue and in vascular organs such as the lung, liver and spleen (Cheng, 2010; Roberts, 2010; Vancouver Island Health Authority, 2006). Amiodarone has a particularly long half-life (40 to 55 days) when given IV and up to 142 days when taken orally (Cahoon et al., 2007; Roberts, 2010). Similar to other lipid soluble medications (e.g., digoxin, fentanyl, coumadin, benzodiazepines and most psychotropic agents), the elderly are especially prone to toxicity. With normal age-related body changes, individuals who are 75 years of age or older have a higher ratio of adipose tissue in relation to lean muscle mass, irrespective of body weight (Cahoon et al., 2007; Waters, 2002). Oral administration requires the patient to have 12 lead ECGs periodically, so that bradycardia, heart blocks and the QTc can be monitored.

4. Are there additional clinical considerations?
Amiodarone potentiates many commonly used medications including warfarin, thyroid medications, digoxin and haloperidol. Warfarin dosages usually require a reduction of 33% to 50% and digoxin may need to be discontinued or the dose reduced by 50% (Cahoon et al., 2007). Electrolytes, thyroid function (hypo/hyperthyroidism), liver function, digoxin levels and prothrombin time international normalized ratio levels need to be monitored with increased vigilance. Clinicians need to be reminded of how long the drug remains in the tissues even after discontinuation. When amiodarone is used in doses of ≤ 400 mg/day, the incidence of TdP is extremely rare (Roberts, 2010; Siddoway, 2003; Vancouver Island Health Authority, 2006). However, this potentially lethal arrhythmia can still occur in settings of low magnesium levels, severe hypokalemia or if the patient is also taking a class I antiarrhythmic drug such as procainamide, propafenone or flecainide (Roberts, 2010; Vancouver Island Health Authority, 2006). Other potential serious side effects include highly morbid pulmonary toxicity, photosensitivity, corneal deposits, optic neuropathy, slate-blue discoloration of the skin and liver toxicity (Cheng, 2010; Goldschlager et al., 2007; Siddoway, 2003).

Summary

Amiodarone remains one of the most commonly prescribed antiarrhythmics effectively treating atrial fibrillation and ventricular arrhythmias. Diligent monitoring for potentially serious side effects especially in the elderly is paramount. ♥

About the Authors

Dorothy Morris, RN, MA, CCN(C), Clinical Nurse Educator Cardiovascular Unit and Coronary Care, Royal Jubilee Hospital, Victoria, British Columbia. Health Promotion and Advocacy Director, Canadian Council of Cardiovascular Nurses.

Nancy Cameron, RN, BScN, CCN(C), Nurse Clinician, Atrial Fibrillation Clinic, Royal Jubilee Hospital, Victoria, British Columbia.

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Ginette Turbide, inf., M.Sc., Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ).

Julie Houle, inf., Ph.D., Professeure, Département des Sciences infirmières, Membre du Laboratoire de recherche en santé cardiovasculaire et métabolique, Université du Québec à Trois-Rivières.

Marie-Ève Leblanc, inf., M.Sc., Ph.D.(c), Sciences pharmaceutiques, Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ).

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Saviez-vous?

Pourquoi l'amiodarone nécessite une surveillance rigoureuse?

Dorothy Morris, inf., MA, CCN(C) et Nancy Cameron, inf., B.Sc.inf., CCN(C)

Questions cliniques courantes et considérations pour la pratique

1. Un des principaux effets secondaires de l'amiodarone est un intervalle QT prolongé, ce qui peut engendrer un effet pro-arythmique. Qu'est-ce qui peut être considéré comme un intervalle QT allongé?

Hommes > 44 secondes ou 440 millisecondes
Femmes > 46 secondes ou 446 millisecondes

2. Y a-t-il des situations qui augmentent le risque de « Torsades de pointes » (TdP), une arythmie ventriculaire, lorsque l'amiodarone est administrée?

La présence de deux facteurs de risque importants et plus, parmi les exemples mentionnés ci-dessous, serait nécessaire pour la survenue potentielle de « Torsades de Pointes » (Vancouver Island Health Authority, 2006; Woosley, 2011).

Facteurs de risques importants

Anomalies à l'ECG initial:
- Bradycardie marquée
- Onde T anormales, c'est-à-dire >5 mm de hauteur dans les dérivations des membres ou >10 mm dans les dérivations précordiales, grandes et pointues, ou de polarité opposée au QRS
- Intervalle QT prolongé

Médication cardiaque :
- Sotalol
- Quinidine

Médication non-cardiaque
- Antihistaminiques
- Antibiotiques (ex : érythromycine, clarithromycine)
- Antifongiques (ex : fluconazole)
- Antipsychotiques (ex : halopéridol, loxapine)
- Antidépresseurs (ex : inhibiteurs sélectifs de la réabsorption de la sérotonine tels que célexa ou paxil, inhibiteurs sélectifs de la réabsorption de la norépinéphrine tels que l'effexor ou cymbalta ou les tricycliques, tels que l'élavil ou imiprex)
- Antiépileptiques (ex : phénytoïne, carbamazépine)

Autres
- Femme
- Maladie affectant la structure cardiaque
- Âge avancé

3. Quels sont quelques unes des propriétés uniques de l'amiodarone et pourquoi les cardiologues maintiennent parfois l'administration de cette médication en présence d'un intervalle QT prolongé?

L'amiodarone est une médication antiarythmique unique, contenant de l'iodine, liposoluble et se liant fortement aux protéines, et qui comporte des caractéristiques électrophysiologiques communes à chacune des classes d'antiarythmiques (Cahoon, Flattery, & Hess, 2007; Palatnik, 2008; Roberts, 2010, Siddoway, 2003). Elle interfère en agissant sur plusieurs canaux d'ions de conduction du myocarde, en agissant comme un bloqueur des canaux sodiques (classe I), un bêta-bloquant (classe II), un bloqueur des canaux potassiques (classe III) et des canaux calciques (classe IV) (Palatnik, 2008; Roberts, 2010). Puisque l'un des principaux effets de l'amiodarone étant le blocage des canaux potassiques, on l'a classé comme agent antiarythmique de classe III (Cheng, 2010; Palatnik, 2008; Siddoway, 2003). Le blocage des canaux potassiques peut prolonger l'intervalle QT et favoriser le développement d'une arythmie ventriculaire appelée « Torsades de Pointes ».

L'administration de l'amiodarone doit être surveillé de près, particulièrement si utilisée en concomitance avec d'autres médications prolongeant l'intervalle QT ou encore lorsque la condition clinique du patient le rend plus à risque de développer cette anomalie (exemples : bradycardie ou débalancement électrolytique) (Cahoon et al., 2007; Roberts, 2010; Vancouver Island Health

Authority, 2006). En assurant toujours une surveillance soutenue de l'intervalle QT lors de l'administration de l'amiodarone, ses autres propriétés antiarythmiques de bêta-bloquants et de bloqueur des canaux calciques et sodiques permettront généralement d'éviter l'apparition de « Torsades de Pointes » (Goldschlager et al., 2007; Roberts, 2010; Siddoway, 2003; Vancouver Island Health Authority, 2006). En évaluant les risques versus les bénéfices de poursuivre l'administration de l'amiodarone, les cardiologues vont parfois diminuer le dosage et corriger les autres conditions cliniques ayant un impact sur l'intervalle QT.

Lorsque l'amiodarone est administrée par voie intraveineuse (IV), ses premiers effets sont ceux reliés aux bêta-bloquants suivis des autres effets, moins importants, associés aux propriétés antiarythmiques sur le blocage des canaux sodiques, potassiques et calciques (Vancouver Island Health Authority, 2006). L'amiodarone IV est un produit vésicant et requiert un filtre de 0,22 micron en tout temps, lors de l'administration intermittente ou continue (Vancouver Island Health Authority, 2010). La filtration de la médication peut toutefois être reportée lorsque la situation laisse présager un arrêt cardiaque imminent et qu'un dosage IV direct est requis. L'administration IV nécessite le monitoring de l'ECG en continue et la mesure fréquente de la pression artérielle car il y a des risque d'hypotension (Cahoon et al., 2007; Vancouver Island Health Authority, 2010).

Lorsque l'amiodarone est administrée par voie orale, elle a davantage d'effets sur le blocage des canaux calciques, sodiques, et en particulier potassiques (Cahoon et al., 2007; Vancouver Island Health Authority, 2006). L'effet antiarythmique maximal peut nécessiter de 3 à 6 semaines suivant l'initiation de la médication puisque celle-ci s'accumule dans les tissus adipeux et les organes vascularisés tels que les poumons, le foie et la rate (Cheng, 2010; Roberts, 2010; Vancouver Island Health Authority, 2006). L'amiodarone comporte une demi-vie particulièrement longue (40 à 55 jours) lorsque administrée IV et jusqu'à 142 jours lorsque administrée par voie orale (Cahoon et al., 2007; Roberts, 2010). Les personnes âgées sont particulièrement vulnérables aux effets toxiques, tout comme pour les autres médications liposolubles (par exemple la digoxin, le fentanyl, le coumadin, les benzodiazépines et la plupart des agents psychotropes). Dans le contexte des changements physiologiques normaux du vieillissement, les individus âgés de 75 ans et plus ont un ratio plus élevé de tissus adipeux en comparaison avec la masse musculaire, et ce, peu importe le poids corporel (Cahoon et al., 2007; Waters, 2002). L'administration par voie orale nécessite un monitoring périodique de l'ECG à 12 dérivations, afin de surveiller la bradycardie, les blocs et l'intervalle QT.

4. Y a-t-il des considérations cliniques additionnelles à considérer?

L'amiodarone potentialise plusieurs types de médication fréquemment utilisées telles que la warfarine, les agents thyroïdiens, le digoxin et l'halopéridol. Le dosage de la warfarine nécessitera habituellement une réduction de l'ordre de 33 à 50% et le digoxin pourra parfois être cessé ou son dosage diminué de 50% (Cahoon et al., 2007). Les électrolytes, la fonction thyroïdienne (hypo/hyperthyroïdisme), la fonction hépatique, la digoxinémie et le temps de prothrombine (ou rapport international normalisé [RNI]) doivent être dosés avec une vigilance accrue. Il est également important de rappeler aux professionnels de la santé de la période de temps pendant laquelle l'amiodarone demeure dans les tissus même après l'arrêt de la médication. Quand celle-ci est utilisée à des doses de moins de 400 mg/jour, l'incidence des « Torsades de Pointes » est assez rare (Roberts, 2010; Siddoway, 2003; Vancouver Island Health Authority, 2006). Toutefois, ce type d'arythmie ventriculaire létale peut survenir en présence d'hypomagnésémie, d'hypokaliémie ou lorsque le patient prend une médication antiarythmique de classe I comme la procaïnamide, le propafénone ou la flécaïnide (Roberts, 2010; Vancouver Island Health Authority, 2006). Les autres effets secondaires graves sont une forte toxicité pulmonaire, la photosensibilité, les dépôts cornéens, les neuropathies optiques, la décoloration bleu-gris de la peau et la toxicité hépatique (Cheng, 2010; Goldschlager et al., 2007; Siddoway, 2003).

Résumé

L'amiodarone demeure un des traitements antiarythmique qui est le plus fréquemment prescrit afin de corriger efficacement la fibrillation auriculaire et les arythmies ventriculaires. Une surveillance rigoureuse des effets secondaires doit être faite, particulièrement lorsqu'il s'agit de patients âgés. ♥

Les auteurs

Dorothy Morris, inf., MA, CSIC(C), Infirmière clinicienne enseignante, Unité cardiovasculaire et soins coronariens, Hôpital Royal Jubilee, Victoria, Colombie Britanique. Directrice Nationale de la promotion de la santé, Conseil canadien des infirmières et infirmiers en soins cardiovasculaires.

Nancy Cameron, RN, B.Sc.Inf., CSIC(C), Infirmière clinicienne, Clinique de fibrillation auriculaire, Hôpital Royal Jubilee, Victoria, Colombie Britannique.

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Canadian Council of Cardiovascular Nurses
202–300 March Road
Ottawa, ON K2K 2E2
Tel: (613) 599-9210
Fax: (613) 595-1155
www.cccn.ca

David Miriguay
Executive Director
Canadian Council of Cardiovascular Nurses
david@cccn.ca

Kathryn Cyr
Administrator
Canadian Council of Cardiovascular Nurses
kathryn@cccn.ca

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Date d'examen : **12 avril, 2012**

Adherence to Prescribed Exercise and Diet Regimens Two Months Post-Cardiac Rehabilitation

Carrie J. Scotto, RN, PhD, Donna J. Waechter, PhD, and James Rosneck, RN, MS, FAACVPR

Background: Adherence to diet and exercise regimens significantly limits morbidity and mortality for cardiac patients. Research at six and 12 months post CR program indicates that healthy behaviours learned in CR are not sustained. However, little is known about the extent of adherence in the immediate program completion period.

Purpose: To determine CR participants' knowledge of their diet and exercise prescription and the degree of adherence two months after completing CR, and to examine demographic and clinical variables to identify relationships to adherence behaviours.

Methods: Participants (n=174) were recruited from Phase II CR over a one-year period. The Diet Habit Survey (DHS) and Duke Activity Status Index (DASI) scores were administered at admission, discharge, and two months post discharge. Structured telephone interviews were conducted to evaluate adherence behaviours. Spearman correlation was used to determine relationships between demographic and clinical variables and adherence behaviours.

Results: Repeated measures ANOVA showed DHS and DASI scores were significantly higher at discharge ($p<0.001$) without significant drift at two months post program ($p<0.09$). These scores were in contrast with low self-report of knowledge of dietary and exercise recommendations and adherence to dietary and exercise instructions. Lower knowledge about diet and exercise were correlated with employment (diet, $p<0.001$; exercise, $p<0.025$). Decreased dietary adherence was correlated with BMI ($p<0.005$). Exercise adherence was correlated with gender ($p<0.021$) and marital status ($p<0.042$).

Conclusion: Although CR participants gain and retain knowledge about necessary dietary changes and improve their exercise activity tolerance during CR, most fail to translate the information into health promoting behaviour changes beginning in the immediate discharge period. Research to identify methods that transform knowledge into lasting behaviour change post CR is needed.

Address for correspondence: Carrie J. Scotto, RN, PhD, 2688 Cardington Green, Uniontown, Ohio 44685. Cell: 330-414-6746; Fax: 330-972-5737; Email: cscotto@uakron.edu

Key words: Cardiac rehabilitation, dietary adherence, exercise adherence, chronic disease management

Adhérence à la diète et à la prescription d'exercice deux mois après une réadaptation cardiaque

L'adhérence à la diète et à l'exercice réduit significativement la mortalité et la morbidité chez les patients cardiaques. La recherche démontre que les comportements de santé appris au cours de la réadaptation cardiaque ne sont pas maintenus à 6 et à 12 mois après le programme. Cependant, il existe peu de connaissance sur le niveau d'adhérence dans la période immédiate après avoir complété un programme.

Buts : Identifier les connaissances des participants en regard de leur diète et la prescription d'exercice ainsi que le niveau d'adhérence deux mois après avoir complété la réadaptation cardiaque. Explorer les variables démographiques et cliniques en lien avec l'adhérence aux comportements.

Méthodes : Les participants (N=174) ont été recrutés à partir de la phase II de la réadaptation cardiaque, sur une période d'un an. Le Diet Habit Survey (DHS) et le Duke Activity Status Index (DASI) ont été administrés à l'admission, lors du congé et deux mois après le congé. Des entrevues téléphoniques structurées ont été réalisées pour évaluer l'adhérence aux comportements. Une corrélation de Spearman a été utilisée pour examiner la relation entre les variables démographiques, cliniques et l'adhérence aux comportements.

Résultats : Des analyses de variances à mesures répétées (ANOVA) ont démontré que les données obtenues à partir du DHS et du DASI étaient significativement plus élevées au congé ($p<0,001$), sans diminution significative observée deux mois après le programme ($p<0,09$). Ces résultats diffèrent avec le fait que les patients rapportent un faible niveau de connaissances sur les recommandations en regard de la diète et de l'exercice et sur l'adhérence à ces recommandations. Un faible niveau de connaissances en regard de la diète et de l'exercice était associé avec le statut d'emploi (diète, $p<0,001$, exercice, $p<0,025$). Un faible niveau d'adhérence en regard de la diète était associé avec l'indice de masse corporelle ($p<0,005$). L'adhérence à l'exercice était associé avec le genre ($p<0,021$) et le statut social ($p<0,042$).

Conclusion : Bien que les patients font l'acquisition de connaissances sur l'importance d'adopter une diète et d'améliorer leur tolérance à l'exercice au cours de la réadaptation cardiaque, la plupart d'entre eux sont incapables de traduire ces informations afin de modifier leurs comportements de santé au cours de la période immédiate après le congé. Il est important de poursuivre les recherche afin d'identifier les méthodes permettant d'intégrer ces connaissances à des modification de comportements durables après la réadaptation cardiaque.

Background

Management of cardiac disease is a significant problem for the 81 million patients and their health care providers in the United States. Initial and repeat hospital admissions for cardiac disease exceed six million each year at a cost of $393.5 billion U.S. Mortality rates exceed 900,000/year (American Heart Association, 2010). Furthermore, cardiac disease produces deterioration in quality of life, decreased physical ability, and impaired family and social roles, and emotional well-being.

To address acute and chronic problems associated with cardiac disease, complex treatment plans have been developed consisting of dietary adjustments, medication education, and balancing physical activity with disease symptoms. Such plans include cardiac rehabilitation (CR) programs that are designed to have a positive effect on recovery from acute cardiac events, as well as subsequent morbidity and mortality for those with cardiac disease (American Association of Cardiovascular and Pulmonary Rehabilitation, 2006; Balady et al., 2007). CR includes supervised physical training sessions that are combined with disease management educational classes related to the life-style, diet, exercise, and medication balance that is essential for recovery. CR has been shown to improve patients' health by promoting strength and endurance, weight control, mental health, quality of life, cognition, and general knowledge of cardiac problems (Ather et al., 2007; Evangelista, Berg, & Dracup, 2001; Gunstad et al., 2007; Haskell et al., 1994; Josephson, Casey, Waechter, Rosneck, & Hughes, 2006).

Rates of adherence to prescribed exercise after CR have been reported from 15% to 65%. A study of 131 people post CR showed 65% maintained an increase in regular activity after one year (Macchi et al., 2009). Leong, Molassiotis, and Marsh (2004) surveyed 52 patients two years after completing a CR program and found only 34.6% maintained the recommended exercise routine. Various aspects of post CR adherence were examined in another study of 37 participants. After one year, 67.5% engaged in moderate exercise while only 37.8% maintained vigorous exercise (Bock, Carmona-Barro, Esler, & Tilkemeier, 2003). Other researchers have reported that only 15% to 50% of people who complete a CR program self-report that they are still exercising after six months and even fewer after a year (Bethel, 1999; Millen & Bray, 2009; Moore et al., 2006).

Post CR dietary adherence has been examined less frequently and tends to focus on a particular aspect of diet such as a decrease in fat intake. For example, Daubenmier et al. (2007) conducted a multisite U.S. study of more than 700 patients and reported a significant reduction in dietary fat intake three months after CR. Scandinavian researchers compared the impact of individual counselling to a control group in 176 CR patients and found no significant difference in dietary adherence between the groups. After six months, both groups had increased use of fish and vegetables, and decreased in saturated fats (Mildestvedt, Meland, & Eide, 2007). Koelewwjin-van Loon et al. (2009) studied 615 patients and compared lifestyle outcome differences between a group of CR patients receiving a nurse-led education intervention and a control group. Although the intervention did not yield significant improvements over the control group, there was a small increase in consumption of vegetables and fat for both groups overall. Hämäläien et al. (2000) studied 15 males one year after coronary surgery who had subsequent diet counselling. Total fat, saturated fats, and cholesterol intake increased significantly by 21%, 36% and 51% respectively. Hartwell and Henry (2003) evaluated the effects of diet counselling and reported only half of the 48 patients were able to maintain a low-fat diet after six months.

Lack of adherence to a prescribed regimen of diet and activity is the most common cause of worsening symptoms, hospital readmission, and mortality for people with cardiac disease (Dunbar-Jacobs et al., 2002; Futterman & Lemberg, 2001; Glazer, Emery, Frid, & Banyasz, 2002; World Health Organization, 2003). The wide range of variables affecting adherence and lack of consistency in measurement may explain, in part, why a clear and accurate picture of the extent and nature of the problem has not emerged. Significant lapses in adherence exist at six to 12 months post CR. In this study, the researchers focused on adherence rates in the immediate post CR period to determine if the problem exists earlier or develops over time.

Purpose

The purpose of this study was to determine CR participants' knowledge of their diet and exercise prescription and the degree of adherence to diet and exercise two months after completing CR. Additionally, demographic and clinical variables were examined to determine their relationship to adherence. These variables included age, race, sex, education, employment, marital status, referring diagnosis, body mass index (BMI), weight loss recommendation, and ratings of recent exercise routine and stress levels.

Methods

Design and setting. In this study the researchers compared pre-program, end-program, and two months post-program scores for diet habits and exercise tolerance. Structured telephone interviews were conducted to gather information about the participants' knowledge of and adherence to recommended diet and exercise prescriptions two months after program completion. After receiving approval from the hospital internal review board a convenience sample of 174 Phase II CR participants at a Midwestern United States hospital-based program were recruited over one year.

The phase II program runs over 12 weeks and provides supervised exercise sessions and classroom educational sessions to promote understanding of cardiac disease and appropriate diet, exercise, and medication treatment. Information about the study was presented during a regularly scheduled educational session. Those who wished to participate had the opportunity to ask questions before giving written consent.

Participants. The participants were English-speaking men and women over the age of 21 enrolled in CR and accessible by telephone for follow-up. Enrolment in the program indicates that the participants experienced a serious cardiac event, either acute coronary syndrome (ACS), myocardial infarction (MI), and/or cardiac surgery.

Sampling methods. The program records were accessed for the following data: 1) weekly dietary habit scores on admission and after completing the program, 2) exercise tolerance scores on admission and after completing the program, 3) demographic variables including age, race, sex, education, employment, marital status, and referring diagnosis, 4) clinical variables including body mass index (BMI), weight loss recommendation, and admission ratings of recent exercise routine and stress levels, and 5) dietary and exercise recommendations received at discharge.

Two months after completing the program, participants received a packet in the mail reminding them about the study and providing instructions for completion of the protocol. The packet included survey tools to measure current weekly diet habits and exercise tolerance. The packet also included an invitation to request a convenient time to receive an interview call. Structured telephone interviews conducted by the primary researcher yielded information about the participants' diet and exercise knowledge and habits at two months post CR.

Variable measures. The Diet Habit Survey (DHS) is a measure of usual weekly diet practices. It is a comprehensive tool, covering five food groups, beverages, salt intake, restaurant eating, and alteration of recipes. The DHS is a valid and reliable tool that was designed to identify eating habits and measure dietary changes made over time (Conner et al., 1992). Test-retest coefficients have been reported as 0.60–0.87. Correlation with cholesterol levels over five years was reported as 0.42.

Exercise activity tolerance was estimated using the Duke Activity Status Index (DASI). The DASI has been shown to have an equitable correlation with maximum oxygen consumption ($r=0.81$) at peak exercise and is a good estimate of functional capacity (Hlatky et al., 1989). Scores are calculated in terms of energy expenditure during prescribed exceptional activities and are expressed in metabolic equivalents of task (METs). One MET is equal to the metabolic rate at rest. MET values of physical activities range from 1.0 (sleeping) to 26 (running) (Ainsworth et al., 2000). Both the DHS and the DASI were administered before beginning the program, on program completion, and again two months after program completion.

Recent exercise routine and stress levels are evaluated on admission. The patient and the staff member discuss the patient's usual activity, risk factors, and life stresses. The staff member assigns a score of "sedentary" for those who have no exercise beyond basic activities of daily living, "active" for those whose lifestyles include occasional work or recreational activity such as walking, gardening, or golf less than three times weekly, and "aerobic" for who engage is specific exercise activity at least three times per week. Stress levels are assigned as "low" for patients who indicate stress is not affecting their daily life, "medium" for those who indicate stress as a factor negatively affecting their daily life and "high" for patients whose stress level is disrupting events of daily life.

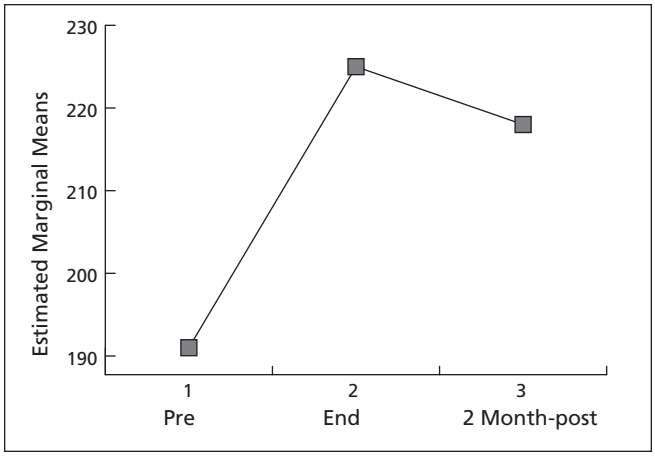

Figure 1: Comparison of Means for Diet Habit Survey. Significant increase between pre and end program ($p<0.001$) for the group. Two months post-program scores decreased, but not significantly ($p<0.085$).

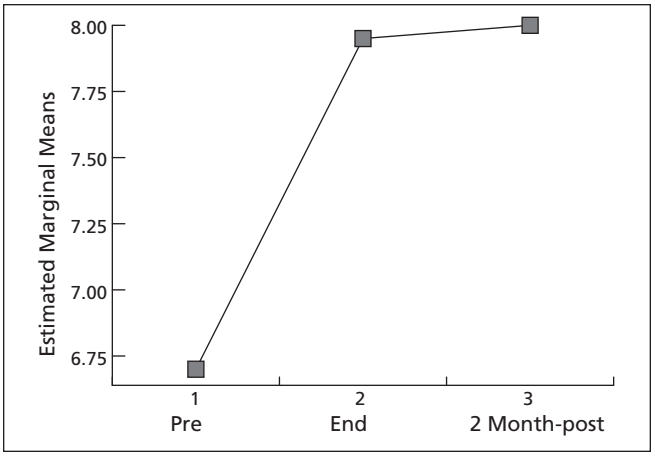

Figure 2: Comparison of Means for Duke Activity Status Index. Significant increase between pre- and end-program scores ($p<0.001$) for the group. Two months post-program scores increased slightly, but not significantly ($p<0.079$).

During the telephone interviews, the participants responded to questions about their knowledge of the diet and exercise prescriptions at discharge and their current adherence to the recommendations. Knowledge of diet was recorded as "all" for those who were able to accurately describe dietary changes recommended at discharge, "some" for those able to relate only generalities about the diet prescription such as "less fat", "less red meat", and "none" for those unable to state any information about their diet recommendations. They were then asked how many times per week they consciously strayed from their diet. Knowledge of exercise prescription was recorded as "all" for those who could state the exercise recommendations received at discharge, "some" for those who gave incomplete answers such as "a couple times a week", and "none" for those who did not know the prescribed amount. Participants were then asked to state the number and length of exercise sessions per week they performed.

Data analysis. Descriptive statistics were calculated to describe the group characteristics and adherence rates. Continuous variables were calculated as means with standard deviations (SD). Nominal variables were calculated as percentages. The pre-program, end-program, and two months post-program DHS and DASI scores were examined using repeated measures ANOVA, with Bonferroni correction for post hoc tests. The relationships between demographic and clinical variables and the adherence variables were examined using Spearman correlation analysis. The significance level was set at 0.05.

Table 1: Descriptive statistics for participants (n = 174)	
Mean Age	66 (SD 10.5)
Sex	
Male	113 (65%)
Female	61 (35%)
Race / Ethnicity	
Caucasian	167 (93%)
African American	7 (4%)
Employed	66 (38%)
Years of Education	13.8 (SD 2.6)
Marital Status	
Married	122 (70%)
Divorced	15 (8%)
Widow(er)	24 (14%)
Single	14 (8%)
Referring Diagnosis	
Coronary Artery Bypass	65 (37%)
Myocardial Infarction	52 (30%)
Stent Placement	47 (27%)
Valve Replacement	10 (6%)

Results

Of 174 participants, 111 (64%) completed the entire protocol. One hundred and fourteen (65%) returned the surveys and 137 (79%) completed the follow-up call. Table 1 shows demographic statistics for the group that indicate this group represents the typical profile of CR participants in the U.S. (American Heart Association, 2010). Descriptive statistics for the clinical variables are listed in Table 2. The average BMI for the group was in the overweight category. The mean recommended weight loss at admission was 24.3 pounds, and the large standard deviation indicated a wide range of weight loss goals. Pre-program exercise routines indicated most participants engaged in some activities prior to the program but did not pursue a formal exercise routine and stress levels were rated as low or medium for most participants.

Dietary adherence. The DHS scores were examined in order to determine changes in usual weekly diet practices. (See Figure 1.) Pre-program scores (mean 191) compared to end-of-program scores (mean 225) improved significantly ($p < 0.001$) for the group. Two months post-program DHS scores (mean 218) compared to end-of-program DHS scores showed healthy diet practices had decreased, but not to a significant extent ($p < 0.085$).

Table 2: Clinical variables for participants	
Body Mass Index	31.2 (SD 5.8)
Recommended weight loss	24.3 (SD 25.6)
Recent Stress	
Low	67 (39%)
Medium	65 (37%)
High	41 (24%)
Recent Exercise Routine	
Sedentary	61 (35%)
Active	81 (47%)
Aerobic	32 (18%)

Participants reported information about their daily adherence to recommended diet changes during follow-up telephone interviews. Information from the discharge summary about dietary recommendations was compared to the participants' responses to interview questions (Table 3). Despite the improvement and maintenance of DHS scores, 87 respondents (64%) were able to relate only generalities about recommended diet changes and 18 (13%) were unable to recall any dietary recommendations. When asked to quantify the number of times they knowingly strayed from their diet each week, consciously making a choice to eat something they know they shouldn't, 96 (70%) strayed between three and six times per week. Those with better knowledge of diet recommendations were less likely to stray from the diet ($r = 0.-456$, $p < 0.001$). Those who were employed had lower knowledge of diet ($r = 0.-174$, $p < 0.021$), and those with higher BMI reported consciously straying from the diet more frequently ($r = 0.155$, $p < 0.005$).

Exercise adherence. The DASI scores were examined in order to determine changes in exercise tolerance and functional capacity. (See Figure 2.) Pre-program scores (mean 6.7) compared to end-of-program scores (mean 7.9) improved significantly ($p < 0.001$) for the group. Two months post-program DASI scores (mean 7.8) compared to end-of-program scores showed exercise tolerance and functional capacity had not changed significantly ($p < 0.079$).

Participants reported information about their adherence to their recommended exercise program during follow-up telephone interviews. Information from the discharge summary about exercise recommendations was compared to the participant's responses to interview questions. Table 4 lists the outcomes for the exercise adherence variables. Despite the improvement and maintenance of DASI scores, 70 (51%) participants were able to only approximately describe exercise recommendations and 23 (17%) were unable to recall any exercise recommendations. When asked how often each week they exercised, 62 (45%) exercised at the most commonly recommended rate of three to four times per week, and 53 (39%) reported two or less sessions per week. Session length was reported at 30 minutes or greater for 100 (73%).

Those with better knowledge of recommended exercise regimen tended to exercise more frequently ($r = 0.677$, $p < 0.000$) with longer sessions ($r = 0.473$, $p < 0.000$). Those who were employed had less knowledge of exercise recommendations ($r = -0.168$, $p < 0.025$). Shorter exercise sessions were also correlated with being female ($r = -0.189$, $p < 0.013$), and being married ($r = -.149$, $p < 0.042$).

Discussion

The results of this study are limited by single site data collection. Multisite studies are needed to corroborate the findings.

Comparison of the DHS scores indicated that participants learned a great deal about the best diet patterns for promoting recovery and health during the program. Scores two months after program completion indicate participants had retained the dietary knowledge. However, this did not ensure knowledge of the

Table 3: Dietary knowledge and adherence

Know Diet Prescription	
All	32 (23%)
Some	87 (64%)
None	18 (13%)
Times Stray per Week	
0–2	17 (12%)
3–4	49 (36%)
5–6	47 (34%)
7–10	14 (10%)

Table 4: Exercise knowledge and adherence

Know Exercise Prescription	
All	44 (27%)
Some	70 (51%)
None	23 (17%)
Exercise Session per Week	
7	1 (1%)
5–6	21 (15%)
3–4	62 (45%)
1–2	25 (18%)
0	28 (21%)
Minutes per Session	
60+	3 (2%)
50–60	35 (25%)
40–45	24 (18%)
30	38 (28%)
10–20	9 (6%)
0	28 (21%)

recommended dietary changes or the practice of dietary changes post program. Only 23% of the group was able to clearly relate the details of their recommended diet changes during the telephone interview.

When confronted with the survey tool for the third time, the participants were able to make healthy choices, and it is somewhat encouraging to note that those with better knowledge were more consciously aware of making poor choices. However, there is incongruence between the knowledge reported on the formal survey tool and the participants' ability to articulate dietary changes and to adhere to those changes.

DASI scores at pre- and end-program indicated that participants significantly increased their exercise tolerance during the program and were able to maintain the improvement two months after completion. The DASI scores represent activities that the participants believe they can carry out, but do not measure what is actually undertaken by the individual. High DASI scores did not ensure that participants had knowledge of recommended exercise or that they were carrying out the instructions. Only about a third of the group was able to accurately state the exercise routine prescribed at discharge. Participants with better knowledge of their exercise recommendations were more likely to exercise. However, less than half exercised at the recommended rates.

The increase and maintenance of dietary knowledge and physical ability post program is encouraging. However, rates for diet and exercise adherence were poor. These findings indicate that CR participants possess knowledge, but lack the mechanisms to articulate and translate that knowledge into an effective plan of action and carry out the plan with consistency. The failure to develop strong practices that promote healthy daily diet and exercise habits indicates a need for interventions to improve adherence beginning in the immediate post -R period and perhaps within the CR program itself.

Researchers indicate a gradual transition from onsite to home-based exercise sessions can improve exercise adherence six months post program (Carlson, Johnson, Franklin, & Vander Lann, 2000). Other studies have shown that follow-up with nurse case managers (Debusk et al., 1994; Haskell et al., 1994) and even obtaining the patient's written, signed agreement to follow the prescribed regimen (Oldridge & Jones, 1983) have also been associated with higher adherence rates. These ideas indicate that continued interpersonal involvement and reminder of the commitment promote adherence behaviours. Many CR programs celebrate patients' completion of the program with a graduation ceremony. This might lead the patients to believe they are done with CR and are set to return to life as usual. Considering these ideas, a gradual rather than abrupt ending of Phase II CR combined with follow-up could improve adherence to diet and exercise.

In addition Phase II CR programs need to include elements that promote the translation of knowledge and abilities into a formal and lasting plan. CR programs should continuously emphasize the goal of home self-management. A qualitative investigation of 18 post CR patients reported that patients identified measuring target heart rate and rating of perceived exertion as activities carried out in the context of the CR program in order for the staff to monitor their progress and complete the medical chart. These self-monitoring skills were perceived as being part of the CR program, but not related to home self-management (Scotto, Waechter, & Rosneck, 2009). This way of thinking may apply to other aspects of CR as well. Educational and exercise sessions should be approached from the standpoint of creating a home self-management program so the patient is continually aware that self-management, not program completion, is the ultimate goal.

Because knowledge alone is not sufficient to ensure adherence, other methods are needed to direct participants to develop adherence behaviours that last beyond the program. Self regulation theory provides an avenue to better incorporate the development of a plan for self-management into CR programs. Interventions using action planning and coping planning have been shown to increase adherence to exercise recommendations after CR (Scholz, Sniehotta, Burkert, & Schwarzer, 2007; Sniehotta et al., 2005). These methods direct participants in creating a formal action plan and preplanning methods to avoid issues or events that may interfere with their plan. Because non-adherence is evident in the immediate post-program period. further investigation of these types of interventions is warranted. ♥

About the Authors

Carrie J. Scotto, RN, PhD, Assistant Professor of Nursing, The University of Akron, College of Nursing, Akron, Ohio. Research Associate, Center for Cardiopulmonary Research, Summa Health System, Akron, Ohio 44325.

Donna J. Waechter, PhD, Administrative Coordinator, Center for Cardiopulmonary Research, Summa Health System, Akron, Ohio 44325.

James Rosneck, RN, MS, FAACVPR, Manager, Cardiovascular & Pulmonary Rehabilitation, Director, Center for Cardiopulmonary Research, Summa Health System, Akron, Ohio 44325.

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Development and Validation of a Time and Motion Tool to Measure Cardiology Acute Care Nurse Practitioner Activities

Kelley Kilpatrick, RN, MSc(A), PhD

Background: Acute care nurse practitioners (ACNPs) provide advanced nursing care to patients and families who are experiencing a complex acute, critical or chronic health condition. A clear understanding of ACNP activities may facilitate the deployment of ACNP roles in health care teams. Time and motion studies represent the gold standard to measure clinician work time.

Methods: A time and motion tool to measure cardiology ACNP activities was developed and pilot-tested in two organizations.

Findings: The researcher produced a valid and reliable tool. The inter-observer agreement was 0.94 following the pilot study. A training guide and a training schedule were produced to support the use of the time and motion tool. Each activity was defined to facilitate the coding of ACNP activities.

Conclusion: A validated tool can contribute to our knowledge of ACNP activities and role components, and identify the ACNPs' contributions to patient care and the functioning of the health care team.

Address for correspondence: Kelley Kilpatrick, RN, MSc(A), PhD, 120 56th Avenue, Lachine, Quebec, H8T 3B9. Tel: 514-637-9059; Email: kelley.kilpatrick@uqo.ca

Key words: nurse practitioner, acute care, validation, time and motion, cardiology

Développement et validation d'un instrument de mesure du temps et des déplacements pour évaluer les activités des infirmières praticiennes spécialisées (IPS) aux soins intensifs de cardiologie

Introduction : Les infirmières praticiennes spécialisées (IPS) des soins intensifs prodiguent des soins à la fine pointe des connaissances en soins infirmiers aux patients et à leur famille vivant une expérience de santé complexe aigue, critique ou chronique.

Méthodologie : Un instrument de mesure du temps et des déplacements pour évaluer les activités des IPS des soins intensifs de cardiologie a été développé et validé lors d'un projet-pilote réalisé dans deux organisations.

Résultats : Les chercheurs ont développé un instrument de mesure valide et fiable. La concordance inter-observateur était de 0,94 suite au projet-pilote. Un guide et une cédule de formation ont été conçus pour accompagner l'instrument de mesure du temps et des déplacements. Chacune des activités des IPS des soins intensifs ont été définies afin de faciliter leur codage.

Conclusion : Un instrument de mesure validé peut nous permettre de mieux connaître les activités et le rôle des IPS aux soins intensifs, d'identifier leur contribution dans les soins aux patients et la dynamique fonctionnelle de l'équipe de soins.

Background

Acute care nurse practitioners (ACNPs) provide advanced nursing care to patients and their families who are experiencing a complex acute, critical or chronic health condition (Kilpatrick et al., in press; Kleinpell, 2005). Nurses in advanced practice nursing (APN) roles like ACNPs are trained at the graduate level (Kilpatrick et al., in press), and integrate in-depth nursing knowledge, skills, and experience to meet the patients' and families' health needs (Bryant-Lukosius & DiCenso, 2004). The largest nurse practitioner (NP) workforce in Canada is located in Ontario (Canadian Institute for Health Information, 2010). The most common specialty reported in an Ontario ACNP workforce study is cardiology (Hurlock-Chorostecki, van Soeren & Goodwin, 2008).

Cardiology ACNPs are involved in different aspects of patient care (Hurlock-Chorostecki et al., 2008; Roschkov et al., 2007). APN roles have been developed in in-patient and post-discharge care in heart failure (Delgado-Passler & McCaffrey, 2006; McCauley, Bixby, & Naylor, 2006; Naughton, Cheek, & O'Hara, 2005; Naylor et al., 2004; Staples & Earle, 2004; Thompson & Dykeman, 2007), hypertrophic cardiomyopathy (Hull-Grommesh, 2009); post-operative cardiovascular care (Broers et al., 2006; Meyer & Meirs, 2005), critical care (Pirret, 2008); nurse-led services (Currie, Karwatowski, Perera, & Langford, 2004; Murchie, Campbell, Ritchie, & Thain, 2005; Page, Lockwood, & Conroy-Hiller, 2005), preparation for cardiac catheterization (Stables et al., 2004), and cardiac rehabilitation (Carroll, Rankin, & Cooper, 2007).

ACNPs fill a gap in patient care by using an expanded scope of practice to provide services (DiCenso et al., 2010). The integration of ACNP roles in health care teams has been inconsistent (Thompson & Dykeman, 2007). Managers and health care team members are challenged to understand what cardiology ACNPs are doing in their role and how to develop complementary roles between ACNPs and members of the health care team (Kilpatrick et al., in press). A clear distinction between roles in the team is necessary to highlight each role's distinct contribution to patient care and prevent role overlap among members of the health care team (Davies & Fox-Young, 2002; Lyon, 2004).

Different methods have been proposed to measure clinician work activities. Researchers have assessed APN nurses' activities using self-report measures (Sidani et al., 2000) and work sampling (Duffield et al., 2005; Hoffman Tasota, Scharfenberg, Zullo, & Donahoe, 2003). Work sampling is used to record activities at specific time points and examines the distribution of work activities (Urden & Roode, 1997). Bratt et al. (1999) compared four approaches to measure the use of clinician time and argued that time and motion studies represent the gold standard to measure clinician activities. These authors found that self-report measures are weak methods because they over-estimate contact time with patients and under-estimate the non-productive clinician time. The self-report methods impose a response burden on participants and are subject to report bias (Burke et al., 2000). In addition, work sampling is not useful when studying individual workers or for estimating the duration of activities (Pelletier & Duffield, 2003). The purpose of this article is to describe the development and validation of a time and motion tool and report on the findings of the pilot test to measure cardiology ACNP activities.

Ethical Considerations

Ethics approval was obtained from the participating organizations. Participants were informed of the study purpose and signed a consent form. Participation in the study was voluntary and participants were informed that they could decline to participate or withdraw from the study at any time.

Methods

Setting and sample. The data were collected in two university-affiliated teaching hospitals with ACNPs working in a heart failure clinic and in a surgical unit for patients post coronary artery bypass grafting (CABG). Three ACNPs were recruited for the pilot test. All the ACNPs had completed graduate-level education and specialty-specific training in cardiology. Two ACNPs had been practising as cardiology ACNPs for more than three years. One ACNP had been practising for one year and a half. The purpose of the pilot test was to determine the feasibility of recording the ACNPs' activities as they unfolded, test the inter-observer reliability of the time and motion tool, and determine if the ACNP activities that were included in the tool accurately reflected ACNP role components.

Procedure. The pilot test consisted of two phases. Representative workdays were selected in collaboration with the ACNPs in both organizations. Measurements in each phase were taken one month apart. Two observers shadowed (Fitzpatrick, While, & Roberts, 1996) the ACNPs as unobtrusively as possible. In the first phase of the pilot test 174 minutes of concurrent activity were recorded, and in the second phase 121 minutes of concurrent activity were recorded.

The second observer was a doctoral student in nursing with limited experience in cardiology. The second observer was trained by the principal investigator to use the time and motion tool. A training guide was sent to the second observer one month before the first pilot phase to allow the observer sufficient time to review the tool and the training schedule. A training schedule was set up including a 60-minute training session the week before the pilot study to review definitions (Urden, Stacy, & Lough, 2006) and scoring rules. A 30-minute review was planned the day of the pilot test to review the tool and to answer any questions. A 15-minute practice run was completed before data collection began for the pilot test. A second phase of observation was completed to evaluate the inter-observer reliability following the changes made to the time and motion tool. A second training session was completed with the same observer and focused on the revised ACNP activity definitions. A 15-minute review was done the day of the second phase to review the changes to the tool and to answer any questions. A 15-minute practice run was planned, but the observers decided it was not needed before data collection for the second phase. These data were not included in the estimation of inter-observer reliability.

Each observer independently indicated the start time of each activity, selected the appropriate code number for the observed activity, and then indicated the stop time of each activity. Short comments or reminders could be indicated in a comment box. The comment box was used to give further explanation if the observer used the code number for the item labelled "other" or if the observer was unsure of how to code the observed activity. The items included in the time and motion tool were delineated and sufficiently distinct from one another to prevent misclassification of activities (Fitzpatrick et al., 1996; Pelletier & Duffield, 2003). Each activity could only be classified in one item. The

time and motion tool was divided into one-minute increments. If more than one activity was undertaken during a one-minute observation period, the observers selected the activity that occupied the largest portion of the one-minute interval and coded this activity in the tool. The time of each activity included the time needed to execute the actual task and other related tasks such as hand washing, identifying the patient, providing explanations to the patient or family for the care activity, getting necessary supplies for the activity, and disposing of supplies according to organizational policy. The activities identified in the time and motion tool needed to be sufficiently specific to represent cardiology ACNP activities, and distinguish between activities completed by nurses in other professional roles and activities completed by health care providers in non-nursing professional groups.

Time and Motion Tool Development

The time and motion tool resulted from a review of relevant literature, item generation and categorization of ACNP activities, and an interview with a practising ACNP. A practising ACNP was interviewed for 60 minutes and was asked to describe a typical work day. The ACNP provided feedback on the relevance of the activities to clinical practice, and was asked to identify any additional activities that needed to be included in the time and motion tool. No activities were added to the tool prior to the pilot test.

The validation of the time and motion tool included the development of a training guide that defined seven activity categories, a training schedule for a second observer, a field pilot test, and a cognitive interview (Dillman, Smyth, & Christian, 2009) of the second observer. Each activity category was defined and specific examples of ACNP activities for each category were provided in the training guide. Each category is described in greater detail below in the section related to categorization. Pelletier and Duffield (2003) argue that a successfully designed tool incorporates marked grids, codes, and descriptors that are clearly identified. Each step of the development was carefully planned to enhance the reliability of the tool. The steps are described below.

Item generation. There is a general consensus in the literature that ACNP roles include clinical, educational, administrative, and research components (DiCenso et al., 2010). These role components represent the theoretical underpinnings to describe cardiology ACNP roles and serve as an organizing framework for ACNP activities to be included in the time and motion tool. Studies related to different types of APN roles such as clinical nurse specialists (CNS) were included in the literature review because ACNP and CNS roles in the same specialty share a number of common characteristics (Kilpatrick et al., in press).

The ACNP activities in the clinical role component occur with patients and families at the bedside or away from the patient's bedside (Duffield et al., 2005). The ACNPs also engage in care coordination activities that contribute to the overall functioning of the unit (Sidani et al., 2000). Thus, the ACNP activities included in the clinical role component are categorized as direct, indirect and administrative activities in the time and motion tool to take into account if the activity occurred at or away from the patient's bedside. Duffield and colleagues (2005) examined the time spent by nurses and CNSs in 25 different care activities and found that it was difficult to differentiate between registered nurses and clinical nurse specialist (CNS) roles for direct, indirect and unit-related activities. Registered nurses and CNSs shared activities related to clerical tasks, teaching, in-service rounds, team meetings, verbal reports and handover. No activity related to the research component of an APN role was identified in the Duffield et al. (2005) measurement tool. The following studies summarize key activities to consider for the time and motion tool.

Kleinpell (2005) followed a cohort of ACNPs in a five-year longitudinal study, and reported that ACNPs were performing tasks of increasing complexity and their scope of practice was expanding over time. The ACNPs cited autonomy, greater involvement with patients and families, and collaborative practice agreements with physicians as the most satisfying elements of their expanding practice. The most frequent ACNP activities reported by Kleinpell (2005) included conducting physical examinations, gathering patients' medical histories, writing orders, conducting rounds, initiating transfers and consultations, and preparing patients for discharge.

A number of researchers have examined the treatment and management of heart failure by nurses in APN roles (Naylor et al., 2004; Osevala, 2005; Rasmusson, Hall, & Renlund, 2007). Khunti et al. (2007) examined disease management outcomes in secondary prevention of coronary heart disease and heart failure in primary care using a clustered randomized trial design, and found improved outcomes for blood pressure control, smoking cessation, serum cholesterol control, more complete clarification for unconfirmed diagnosis of heart failure and physical functioning scores. In a randomized control trial (RCT) of transitional care from the hospital to home for elderly heart failure patients, Naylor et al. (2004) found that comprehensive discharge care by an APN decreased the total number of hospitalization days at 52 weeks, increased the length between discharge and readmission or death, and improved quality of life up to 12 weeks following discharge.

Several studies were identified that detailed the care required in heart failure and other forms of cardiac disease (Anthony & Sendelbach, 2007; Davidson et al., 2008; Deaton & Grady, 2004; Idemoto & Kresevic, 2007; MacMahon & Lip, 2002; Reigle, Molnar, Howell, & Dumont, 2006; Tranmer & Parry, 2004). In an overview of outcomes for cardiac surgery patients, Whitman (2004) identified relevant outcomes including early and late mortality rates, physiological measures, hemodynamic stability, GI symptoms, pressure ulcers, surgical wound complications, dysrythmias and pain. Other outcomes included functional status, quality of sleep patterns, activities of daily living and self-care, knowledge related to recovery, diet and exercise, return to work and sexual activity. Family functioning, social support and coping with uncertainty, chest pain, anxiety, and depression pre- or post-surgery were all identified as relevant outcomes (Whitman).

In an RCT with repeated measures, Carroll et al. (2007) identified that elderly unpartnered post-myocardial infarction and post-CABG surgery patients closely followed after discharge with an APN and a peer intervention exhibited higher rates of participation in cardiac rehabilitation programs and a trend was noted for fewer hospitalizations. Following an RCT, Stables et al. (2004) found that ACNPs prepared patients for cardiac catheterization procedures as safely as physician residents, the duration of the pre-admission clinic was shorter and patient satisfaction was higher in the ACNP group. Meyer and Meirs (2005) retrospectively compared post-CABG patients followed by the ACNP and the cardiac surgeon in a collaborative practice model. These authors noted decreased length of stay by an average of 1.91 days and decreased costs per care episode with savings of more than $5,000 U.S. per patient.

The safety and effectiveness of nurse-led services have also been explored. Broers et al. (2006) found that nurse-led follow-up for post-CABG patients is safe and effective and post-CABG patients followed by an ACNP were more satisfied with the communication and the amount of information provided about their care. There was also greater continuity of care, as the ACNP in the study assumed the role of a case manager. Nurse-led cardioversion services have also been developed to reduce wait times for this procedure. Boodhoo and colleagues (2004) evaluated the nurse-administered procedure to be effective, safe and well tolerated by patients. Outcomes included success rate of conversion of arrhythmia at discharge and at six weeks, mean cumulative energy and number of shocks and mean dose of sedation (Boodhoo et al.). The wait times were reduced from three months to four weeks (Boodhoo et al.). Similar positive outcomes were noted in a study by Currie et al. (2004). These authors highlighted that structural constraints in the organization such as the non-availability of beds, theatre time in the operating room or the lack of availability of junior doctors needed to be addressed. Currie et al. (2004) identified process weaknesses that needed to be addressed. They included poor coordination and communication between services, missing anticoagulation results, insufficient imaging services for cardiac echography, and inflexible scheduling of patients that led to procedure cancellations.

Categorization. Overall, 32 activities were generated. The activities were identified following a review of literature and included ACNP activities that affected patient care, and identified cardiology ACNP potential contributions to patient care. These activities were organized into seven categories that included direct care, indirect care, educational, administrative, research, other, and personal activities. Cresswell and Plano Clark (2007) recommend using specific definitions to categorize activities. The nursing work definitions were adapted from the work of Urden and Roode (1997), Sidani and Irvine (1999), Sidani et al. (2000), and Duffield et al. (2005). The definitions provided by Becker, Kaplow, Muenzen, and Hartigan (2006) and Urden et al. (2006) were used to identify ACNP activities. The tool is described in the following sections.

The direct care category included 18 activities of direct patient care performed in the presence of the patient or the family. Examples of direct care activities included physical assessments, history taking, ordering and interpreting laboratory tests, monitoring and prescribing medications, managing cardiopulmonary resuscitation, central venous catheter insertion, therapeutic relationships with patients and families, teaching activities with patients and families, and monitoring the patient's nutritional status.

The indirect care activities were completed for specific patients, but away from the patients' bedside. Three activities were identified in the tool related to documentation, discharge planning and participating or leading patient care rounds. Examples of activities included giving report and communication with other health care providers, completing patient records, participating or leading patient care rounds, and discharge planning. Two educational activities were identified. Educational activities included the formal and informal teaching and learning activities that are completed with members of the health care team. The educational activities could be related to patient care, learning opportunities in complex clinical situations, new technology, technical skills, the development of staff education programs, and coaching activities. Four administrative activities related to administrative

meetings, protocol development such as the development or update of medical directives, and care coordination within the organization or with other organizations were included in the time and motion tool.

Three research activities were identified and included participating in research in nursing and with other disciplines, and the use of research in practice. The research activities included activities such as identifying an issue, reviewing relevant literature, developing a research question or a research proposal, recruitment, data analysis or the development of recommendations. One category for "other" activities was developed for activities that could not be categorized in the time and motion tool. A category for personal time was added for activities not related to patient care such as meals, breaks or personal telephone calls.

Data collection. The data were collected in February 2009 and March 2009. The two observers completed 174 minutes of concurrent observation of one ACNP for the first session. The observation period was extended beyond the original 120 minutes to avoid disrupting the ACNP and patient encounter (See Table 1). The initial plan for the pilot study was to measure alternately the activities of each ACNP. The pilot study quickly brought to light the difficulties of separating the data collection periods, as originally planned, and coordinating the change of measurement of one ACNP's activities with the other ACNP because of ongoing patient care activities. There was an increased risk of interrupting a patient encounter or being unable to measure ACNP activities adequately. A decision was made during the pilot test to complete the measurements with only one ACNP to accurately measure ACNP activities and avoid disrupting patient care encounters. This facilitated the data collection process for all those involved and provided a better picture of a patient care encounter by decreasing the interruptions. Tucker and Spear (2006) have reported observation periods in excess of 13 hours without consequences for participants.

Data analysis. The data were analyzed using Statistical Package for the Social Sciences version 16 (Field, 2005). Descriptive statistics were generated, and the ACNP activities were grouped into categories (Rosenfeld, McEvoy, & Glassman, 2003) to identify cardiology ACNP role components and role enactment (Sidani et al. 2000). The balance of activities across the role components gave an indication whether cardiology ACNP roles were being introduced as physician extender or APN roles and the ACNP's enacted scope of practice (Rosenfeld et al., 2003; Sidani et al., 2000).

Table 1: Time and motion activities during the first portion of pilot test

Category	Activity	Total Minutes	Percent %	Percent %
Direct	Physical exam/assessment	35	20.1	
Direct	Teaching/Education-Patient/family	19	10.9	
Direct	Order/Inter. X-Ray treatment	18	10.3	
Direct	Monitor/prescribe meds (Not IV)	13	7.5	
Direct	Order/ inter. lab tests	12	6.9	
Direct	Nutritional feeding or diet	2	1.1	
Category Total				56.8
Indirect	Participate/lead rounds	16	9.2	
Indirect	Documentation	13	7.5	
Indirect	Discharge planning	4	2.3	
Category Total				19.0
Admin.	Care coordination within org.	42	24.1	
Category Total		42	24.1	24.1
Grand Total		174		99.9*
* ≠ 100% due to rounding				

Results

Inter-observer agreement was estimated using the activities identified at each minute during the data collection period yielding 174 data points. The kappa statistic was calculated to assess the proportion of inter-observer agreement that was achieved beyond chance (Sim & Wright, 2005) by comparing the inter-observer agreement for the 174 data points. The inter-observer agreement, kappa (κ), for the timing and the selection of activities included in the time and motion tool was 0.74. Stemler (2004) recommended a value for the kappa statistic greater than 0.60 to indicate substantial inter-observer agreement. Cognitive interviewing (Dillman et al., 2009) was used to ascertain the second observer's understanding of the items that were selected during the first phase of the pilot test. The definitions for the seven categories included in the training schedule were reviewed and revised following the interview with the second observer. The definitions of the activities were supplemented and specific examples were provided in the training guide. These clarifications helped to further delineate and differentiate each activity.

After the first phase of the pilot test, the activities related to prescribing tests and blood work were condensed into one item, and invasive procedures were regrouped under one item. Both observers identified difficulties categorizing empathic communication that was not related to teaching activities, or working through a specific health problem or issue with the patient or family. An item for supportive communication was added to the tool to capture supportive, empathic or coaching types of ACNP and patient or family communications. This item included the verbal or non-verbal communication with the patients or families that conveyed support and/or empathy, and was not related to a specific teaching or educational activity, or a therapeutic relationship that addressed a specific issue. This type of communication went beyond the social interaction related to the establishment of a conversation and was more holistic in nature.

One hundred and twenty-one minutes of concurrent observations were completed in the second phase of the pilot test. The inter-observer agreement increased to $(\kappa) = 0.94$. Overall, the two observers disagreed on six of 121 observations. The differences were noted in the start and stop times of the activities, which could be accounted for by a difference of a few seconds on the observers' watches. No differences were noted in the selection of ACNP activities. In addition, the communication activities that had been a challenge to identify in the first session of the pilot phase of the study were easier to classify using the revised time and motion tool and definitions. The final tool included 30 items divided into seven categories.

Discussion

The purpose of the pilot test was to test the feasibility of measuring ACNP activities as they unfolded with patients and families, and test inter-observer agreement for the time and motion tool. The sample of activities and time spent in ACNP role components in Table 1 represent a portion of the ACNPs' work activities. Additional ACNP activities were identified in the research role component in the second phase of the pilot test. No activities were identified in the education role component during the pilot test and no time was measured for this role component. This is consistent with the results of previous research (Hurlock-Chorostecki et al., 2008; Roschkov et al., 2007) that found that ACNPs spent less than 20% of their work time in the non-clinical activities including research and education. The activities indicated in Table 1 were measured during routine patient care encounters, which may explain the large amount of time spent in direct, indirect and care coordination activities. The percentage of time spent in the ACNP role components provides an indication if the ACNP role is enacted as a physician extender or an advanced practice nursing role. Researchers have identified a tug-of-war between physicians and nursing managers to focus on the clinical component of the ACNP role (DiCenso et al., 2010). However, the inclusion of the non-clinical role components in a time and motion tool is important because the identification of the non-clinical activities can serve to clarify the added value of ACNP roles in health care teams (Kilpatrick et al., in press).

One of the goals of the pilot test was to determine the feasibility of assessing the ACNP role components from the time and motion study. The ACNP activities were selected following a review of the relevant literature and categorized using theoretically identified ACNP role components. The ACNP activities were measured in minutes and grouped into categories (Pelletier & Duffield, 2003) that included ACNP-specific direct and indirect care, education, administrative, and research activities. The time spent in the different categories can be used to determine how ACNP roles were enacted on a day-to-day basis (Oelke et al., 2008). The observers were able to categorize all ACNP activities during the time and motion pilot test. Definitions for each of the items were developed for the time and motion training guide based on the literature. These definitions enhanced the reliability of the measurement. The pilot study identified activities specific to ACNP practice such as prescribing medications and tests, as well as communication and administrative activities that represented elements of an APN role. The time and motion tool measured the time needed to complete patient care activities and may assist researchers and managers to identify patterns of activities as the workday unfolds.

The first portion of the pilot test identified a challenge for the observers to adequately categorize the ACNP activities related to patient communication. The adjustments made to the time and motion tool facilitated the identification of these activities in the subsequent phase of the pilot test. Effective communication was seen as an essential strategy to provide services to patients and families (Munro & Taylor-Panek, 2007; Vazirani, Hays, Shapiro, & Cowan, 2005), and facilitate working as a team (Bamford & Griffin, 2008; Jones, 2005). Few researchers (Sidani & Doran, 2010; Sidani et al., 2006) have examined how ACNPs affect key processes such as communication and care coordination, and the ACNP's contribution to these processes is not well understood. A measurement tool that identifies activities that include communication with patients and families and care coordination with other providers within and outside of the organization may contribute to our knowledge of ACNP activities and capture key ACNP contributions to patient care and team functioning.

Finally, the selection of the second observer in the validation of a measurement tool is an important consideration. Specific observer characteristics were deemed important to the success of this study (Pelletier & Duffield, 2003). They included the observer's knowledge of nursing and nursing activities, a keen sense of observation, and a willingness to question the coding of nursing activities in the time and motion tool. It was not necessary for the observer to have specialty-specific knowledge in acute care cardiology to recognize specialty-specific activities. The definitions that were elaborated in the training guide and the placement of the comment box directly on the measurement tool facilitated the coding of ACNP activities when the observer did not have specialty-specific knowledge.

Limitations

The use of direct observations may have induced a source of bias known as the Hawthorne effect where participants changed their behaviour as a consequence of being observed (Bowling, 2002). A number of steps were taken to decrease this potential limitation. They included the data collectors remaining as inconspicuous as possible during data collection, and the rigorous training of a second observer. The ACNPs reported no longer feeling under observation after the first hour of direct observation.

Conclusion

The study produced a valid and reliable time and motion tool to measure the activities of cardiology ACNPs in a medical and a surgical setting. The inter-observer agreement (κ) was 0.94 following the pilot study. A training guide and training schedule were produced to support the use of the time and motion tool, and each activity was defined to facilitate the coding of ACNP activities. Such a tool can contribute to our knowledge of ACNP activities and role components, and identify the ACNPs contributions to patient care and team functioning. ♥

About the Author

Kelley Kilpatrick, RN, MSc(A), PhD, Post doctoral fellow with CHSRF/CIHR Chair Program in Advanced Practice Nursing, Professor, Université du Québec en Outaouais, Québec, Canada.

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Clopidogrel and Proton Pump Inhibitors: Is There a Significant Drug–Drug Interaction?

Emilia Shmulevich, RN, Michael Friger, PhD, MA, Harel Gilutz, MD, and Abed N. Azab, RN, PhD

Dual antiplatelet therapy with aspirin and clopidogrel is among the most efficacious treatment for patients after acute coronary syndromes and for those who have had a percutaneous coronary intervention and coronary stent implantation. Patients who are treated with dual antiplatelet therapy are usually also ordered medications that reduce the secretion of gastric acid (such as H_2 receptor blockers or proton pump inhibitors [PPIs]) in order to decrease the risk of gastrointestinal bleeding and dyspepsia. Numerous observational studies reported that omeprazole (a PPI) attenuates the antiplatelet activity and clinical effectiveness of clopidogrel and causes adverse cardiovascular events. Based on these findings, several medical agencies in the world have issued communications regarding the negative interaction between clopidogrel and PPIs, urging clinicians to evaluate the need for starting treatment with a PPI in patients taking clopidogrel. There are studies that reported contradicting findings, suggesting that there is no significant interaction between clopidogrel and PPIs. Only one prospective, randomized, double-blind, placebo-controlled clinical trial examined the interaction between clopidogrel and omeprazole and did not demonstrate cardiovascular harm among the patients who were treated with clopidogrel and omeprazole, as compared to those who were treated with clopidogrel and placebo. In this article, the authors review the current studies that reported a possible drug-drug interaction between clopidogrel and PPIs, particularly omeprazole.

Address for correspondence: *Dr. Abed N. Azab, School for Community Health Professions, Faculty of Health Sciences, Ben-Gurion University of the Negev, P.O. Box 653, Beer-Sheva, 84105, Israel. Phone: (972)-8-6479-561; Fax: (972)-8-6477-683; E-mail: azab@bgu.ac.il*

Clopidogrel et les inhibiteurs de la pompe à proton : Existe-il une interaction médicamenteuse significative?

La double thérapie antiplaquettaire qui inclut l'aspirine et le clopidogrel fait parti des traitements les plus efficaces après un syndrome coronarien aigu et après une intervention coronarienne percutanée avec implantation d'un tuteur coronarien. Les patients traités avec la double thérapie antiplaquettaire prennent habituellement aussi des médicaments prescrits pour réduire la sécrétion d'acides gastriques (tel que les bloqueurs des récepteurs H_2 ou les inhibiteurs de la pompe à proton [IPP]) afin de réduire les risques de saignements gastro intestinaux ou de dyspepsie. De nombreuses études d'observation ont rapporté que l'omeprazole (IPP) atténue l'activité antiplaquettaire et l'efficacité clinique du clopidogrel et cause des événements cardiovasculaires défavorables. Basé sur ces résultats, plusieurs regroupements médicaux dans le monde ont publié des communications en regard de l'interaction négative entre le clopidogrel et les IPP, encourageant les cliniciens à évaluer les besoins avant de débuter un traitement avec un IPP chez les patients qui prennent du clopidogrel. Certaines études ont rapporté des résultats contradictoires suggérant qu'il n'existe pas d'interaction significative entre le clopidogrel et les IPP. Une seule étude prospective (essai clinique randomisé, à double insu, contrôlé avec placebo) a examiné l'interaction entre le clopidogrel et l'omeprazole et n'a pas démontré d'effets néfastes cardiovasculaires chez les patients traités avec le clopidogrel et l'omeprazole, en comparaison des patients traités avec le clopidogrel et le placebo. Dans cet article, les auteurs présentent une revue des études récentes qui ont rapporté une interaction médicamenteuse possible entre le clopidogrel et les IPP, en particulier avec l'omoprazole.

The basis for the hypothetical interaction between clopidogrel and PPIs

Despite the improvement in primary prevention and treatment strategies, cardiovascular diseases remain the leading cause of death in most developed countries. In 2006, cardiovascular diseases accounted for 34.3% of all deaths in the U.S. (831,272 deaths), out of which 51% were due to coronary heart disease (Lloyd-Jones et al., 2010). Atherosclerosis and subsequent thrombosis of coronary arteries are the major factors leading to acute coronary syndromes (ACSs) and coronary death. The mechanisms underlying arterial thrombosis and ACSs are very complex. However, it is known that platelet activation and aggregation play a significant role (Sharis, Cannon, & Loscalzo, 1998).

Antiplatelet drugs (drugs that inhibit platelet activity and aggregation) are among the most established and efficacious treatments for patients with coronary artery disease and ACSs (Steinhubl et al., 2002; Yusuf et al., 2001). Dual antiplatelet therapy with aspirin and clopidogrel is known to significantly reduce the incidence of recurrent cardiovascular events among patients after ACS, particularly in patients who underwent a percutaneous coronary intervention (PCI) (Anderson et al., 2007; Antman et al., 2004; Bassand et al., 2007; Becker

et al., 2009; Bhatt, 2007; Park et al., 2010; Steinhubl et al., 2002; Van de Werf et al., 2008; Yusuf et al., 2001). In patients after a PCI and coronary stent implantation, treatment with clopidogrel (alone or together with aspirin) reduced the incidence of stent thrombosis and other atherothrombotic events (Steinhubl et al., 2002). Consistently, poor adherence or early withdrawal of clopidogrel, especially in a period of seven to 30 days after angioplasty, is associated with increased risk of major adverse cardiovascular events (MACEs) (Ackman, Graham, Hui, & Tsuyuki, 2006; Becker et al., 2009; Ho et al., 2008; Jackevicius et al., 2008; Sheehy, LeLorier, & Rinfert, 2008). For patients who underwent a PCI, dual antiplatelet therapy is ideally recommended for one to 12 months following a bare metal stent insertion, and for 12 months after a drug-eluting stent implantation (Kushner et al., 2009; Park et al., 2010; Van de Werf et al., 2008).

Clopidogrel is a thienopyridine drug that is consumed worldwide. With annual sales of ~9.1 billion U.S. dollars. It was ranked second in the best-selling drugs list in 2009 (IMS Health Midas, 2009). Clopidogrel is a prodrug that requires hepatic metabolism in order to become active (Kim, Park, Hong, & Park, 2008; Mega et al., 2009a; Savi et al., 2000; Savi et al., 2001). Its biotransformation to an active metabolite is carried out in two steps, which are mediated by hepatic cytochrome P-450 (CYP450) isoenzymes (Ackman et al., 2006; Ho et al., 2008; Jackevicius et al., 2008; Mega et al., 2009a; Savi et al., 1994; Sheehy et al., 2008; Simon et al., 2009). The first step involves CYP1A2, CYP2B6 and CYP2C19. The second step comprises CYP2B6, CYP2C9, CYP3A4, and CYP2C19. Therefore, CYP2C19 is the main isoenzyme required for the biotransformation of clopidogrel to an active metabolite (Mega et al., 2009a). It is important to know that approximately 85% of a clopidogrel dose is metabolized to inactive metabolites and only the remaining 15% is metabolized to the active metabolite by CYP450 (Angiolillo et al., 2007; Becker et al., 2009; Clarke & Waskell, 2003; Kazui et al., 2010; Mega et al., 2009a; Pereillo et al., 2002; Savi et al., 2000; Simon et al., 2009).

The active metabolite of clopidogrel is a potent, irreversible inhibitor of platelet $P2Y_{12}$ adenosine diphosphate receptor (Cattaneo, 2010; Savi et al., 1992; Savi et al., 2000; Sharma et al., 2009; Small et al., 2008; Zarowitz, 2009). $P2Y_{12}$ inhibition is associated with dephosphorylation of intra-platelet vasodilator-stimulated phosphoprotein (VASP), resulting in a significant inhibition of platelet aggregation. VASP provides an index of platelet reactivity; the higher the platelet reactivity index (PRI), the more frequently thrombosis occurs (Barragan et al., 2003; Ford, 2009; Gurbel, Becker, Mann, Steinhubl, & Michelson, 2007; Laine & Hennekens, 2010; Sharma et al., 2009). Variations in platelet reactivity have been associated with adverse outcomes after coronary stenting (Barragan et al., 2003; Matetzky et al., 2004).

Due to its major role in the conversion of clopidogrel to its active metabolite, the function of CYP2C19 significantly affects the therapeutic efficacy of clopidogrel. Thus, conditions in which CYP2C19 function is reduced are expected to lead to diminished antiplatelet activity of clopidogrel. In this regard, it is worth noting that the genes encoding CYP isoenzymes are polymorphic and that certain alleles confer reduced enzymatic function. Data regarding *in vitro* metabolism and clinical outcomes suggest that patients with reduced-function CYP2C19 polymorphisms have lower active metabolite levels of clopidogrel and, hence, a lower degree of platelet inhibition (Collet et al., 2009; Ford, 2009; Hulot et al., 2010; Lau et al., 2003; Mega et al., 2009a; Roden & Stein, 2009; Roden & Shuldiner, 2010; Shuldiner et al., 2009; Simon et al., 2009). The presence of loss-of-function alleles (such as CYP2C19*2) may be a risk factor for stent thrombosis and MACEs (Collet et al., 2009; Ford, 2009; Hulot et al., 2010). However, a recent study showed that the presence of CYP2C19 loss-of-function alleles did not affect the therapeutic efficacy of clopidogrel (as compared to placebo) among patients with ACS and atrial fibrillation (Pare et al., 2010). Furthermore, drugs that inhibit the activity of CYP2C19 are also expected to reduce the antiplatelet function of clopidogrel. Many drugs markedly inhibit the activity of CYP2C19 (Wilkinson, 2005) including proton pump inhibitors (PPIs), antidepressants (e.g., fluoxitine, fluvoxamine and moclobemide) ticlopidine, nelfinavir, phenytoin, phenobarbital, fluconazole, ketoconazole, among others.

Patients who are treated with dual antiplatelet therapy are usually also ordered medications that reduce the secretion of gastric acid (such as histamine H_2 receptor blockers and H^+/K^+ ATPase inhibitors; the latter also referred to as PPIs) in order to decrease the risk of dyspepsia, esophagitis, stomach ulcers and gastrointestinal (GI) bleeding (Bhatt et al., 2008; Gilard, Arnaud, Le Gal, Abgrall, & Boschat, 2006; Gilard et al., 2008; Hallas et al., 2006; Laine & Hennekens, 2010). Due to potent inhibition of H^+/K^+ ATPase, PPIs are considered the most efficient inhibitors of gastric acid secretion. PPIs are among the most widely prescribed drugs worldwide (Canadian Agency for Drugs and Technologies in Health, 2010; Ho et al., 2009; Schafer et al., 2008). Five PPIs are available: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole, all of which are substrates of CYP450 (Hoogerwerf & Pasricha, 2006). Similar to clopidogrel, PPIs are prodrugs that require metabolism in order to become active. However, this step is not carried out by CYP450 (Anderson, 1996; Blume, Donath, Warnke, & Schug, 2006; Desta, Zhao, Shin, & Flockhart, 2002; Hoogerwerf & Pasricha, 2006). CYP450 isoenzymes, particularly CYP2C19 and CYP3A4, are involved in the subsequent inactivation of the active metabolites of PPIs. Therefore, a reduction in CYP450 activity will

result in increased levels of the active metabolites of PPIs, enhancing their therapeutic efficacy (Anderson, 1996; Blume et al., 2006; Desta et al., 2002). Each PPI has a different affinity to the various CYP isoenzymes. Omeprazole has the highest affinity to CYP2C19, esomeprazole has a high affinity to CYP3A4, lansprazole and rabeprazole are metabolized by CYP2C19 and CYP3A4, while pantoprazole has a high affinity to CYP2C9 (Blume et al., 2006; Juhasz, Herszenyi, & Tulassay, 2009; Li, Andersson, Ahlstrom, & Weidolf, 2004; Meyer, 1996).

Studies that support the hypothesis that PPIs reduce the antiplatelet activity of clopidogrel

In 2006, Gilard and co-authors reported for the first time that patients who were treated with clopidogrel together with omeprazole had significantly higher VASP values, suggestive of reduced antiplatelet activity (Gilard et al., 2006). The mechanism by which omeprazole is thought to reduce the antiplatelet activity of clopidogrel is through a competitive inhibition of the conversion of clopidogrel to its active metabolite by CYP2C19, leading to lower levels of the active metabolite. Following the study by Gilard et al. (2006), multiple researchers have reported that omeprazole and possibly other PPIs attenuate the antiplatelet activity and clinical effectiveness of clopidogrel (Ching, Li, McKay, Mather, & Lundbye, 2009; Cuisset et al., 2009; Evanchan, Donnally, Binkley, & Mazzaferri, 2010; Gilard et al., 2008; Gupta, Bansal, & Sotos, 2009; Hall et al., 2009; Ho et al., 2009; Juurlink et al., 2009; Laine & Hennekens, 2010; Norgard, Mathews, & Wall, 2009; O'Donoghue et al., 2009; Pezalla, Day, & Pulliadath, 2008; Sibbing et al., 2009; Stanek et al., 2009; Stockl et al., 2010; Sweeny et al., 2009; Yasuda et al., 2009; Yun et al., 2010).

For example, in a prospective, randomized, double-blind study, Gilard et al. (2008) determined platelet reactivity among patients who were receiving clopidogrel following coronary stenting with respect to whether they were or were not also given omeprazole. On the first day (after stenting), the mean PRI was similar in the two groups. In contrast, on the seventh day, the mean PRI was 51.4% and 39.8%, respectively, pointing to a lower antiplatelet activity of clopidogrel when it is given together with omeprazole (Gilard et al., 2008). Sixteen patients (26.7%) in the clopidogrel plus placebo group were considered to be poor responders to clopidogrel, as compared to 39 (60.9%) in the clopidogrel plus omeprazole group ($p<0.001$). The odds ratio (OR) for being a poor responder to clopidogrel when treated with omeprazole was 4.31 (95% confidence interval [CI] 2.0 to 9.2). This was the first established study in which clinicians were advised to be aware of the possibility that omeprazole significantly reduces the therapeutic efficacy of clopidogrel.

Confirming results were obtained in a retrospective cohort study of 14,383 patients (9,862 received only clopidogrel and 4,521 received clopidogrel and a PPI) after coronary stent implantation (Aubert et al., 2008). The incidence of MACEs (hospitalization for stroke, MI, angina or coronary artery bypass graft surgery) within one year of follow-up was 32.5% among the patients who took clopidogrel plus a PPI, as compared to 21.2% in patients who took only clopidogrel (adjusted OR 1.79, CI 1.62–1.97) (Aubert et al., 2008).

Consistently, in a retrospective study, Ho et al. (2009) examined the outcomes of 8,205 patients after hospitalization for ACS, as to whether they were or were not taking a PPI together with clopidogrel. In the group that did not take a PPI, death or rehospitalization for ACS occurred in 20.8% of the patients, as compared to 29.8% of the patients who were treated with a PPI (together with clopidogrel). For the secondary outcomes, the rates of recurrent hospitalization for ACS (14.6% versus 6.9%, $p<0.001$), revascularization procedures (15.5% versus 11.9%, $p<0.001$), and death (19.9% versus 16.6%, $p<0.001$) were higher among patients taking clopidogrel plus a PPI compared to those taking clopidogrel alone (Ho et al., 2009).

Moreover, Juurlink et al. (2009) conducted a population-based case control study of 13,636 patients who were given clopidogrel following hospitalization for acute myocardial infarction (MI) and examined the effect of concurrent treatment with a PPI (omeprazole, lansoprazole, pantoprazole or rabeprazole). It was found that, with the exception of pantoprazole, all PPIs were associated with 40% increase in the risk of recurrent MI within 90 days of hospital discharge (OR 1.40, 95% CI 1.10-1.77). No correlation was found between the use of H_2 blockers and recurrent MI (Juurlink et al., 2009).

Similarly, Hall et al. (2009) observed that the incidence of death and recurrent MI are higher in patients who received both clopidogrel and a PPI (hazard ratio [HR] 1.64, 95% CI 1.41–1.9, $p<0.001$). Surprisingly, omeprazole was associated with the lowest incidence of MI and death, as compared to pantoprazole, which was associated with the highest risk (Hall et al., 2009). The authors concluded that there are probably different mechanisms for clopidogrel resistance and that it is not a CYP2C19(only)-dependent mechanism (Hall et. al., 2009).

In a retrospective study, Sweeny et al. (2009) found that the mortality rate is higher in PPI plus clopidogrel users as compared to PPI non-users (53.5 versus 33 deaths per 1,000 person-year, $p<0.001$; estimated risk 1.30; 95% CI 1.06-1.60). However, no significant risks for stent thrombosis or target lesion revascularization during 30 days were found (Sweeny et al., 2009). Dunn et al. (2008) have also reported that the use of clopidogrel with PPIs

is associated with an estimated risk of death, MI, and target vessel revascularization of 1.63 (p = 0.043) during a follow-up of one year.

The attenuating effect of PPIs on the action of clopidogrel was further established in the retrospective study by Ching et al. (2009). The study included 1,192 post-PCI patients who were treated with clopidogrel, out of which 36% were on a PPI and 64% were not. At nine months of follow-up, death occurred in 3.7% of the clopidogrel-PPI combination group and 1.4% of the clopidogrel-only group (p = 0.11). On the other hand, MACEs occurred in 8.2% versus 4.2% (p = 0.004), respectively. The adjusted OR showed that the effect of PPIs on death was not significant, while the effect on MACEs remained significant (OR 1.76, 95% CI 1.078–2.876, p = 0.024) (Ching et al., 2009). In line with these findings, Gupta et al. (2009) demonstrated that 56% of the patients after PCI who simultaneously took clopidogrel and a PPI (lansoprazole or omeprazole) had MACEs, as compared to 38% of the patients who were treated with clopidogrel alone (p = 0.025). More recently, in a study of patients after a PCI with drug-eluting stent, the investigators compared patients who took the combination therapy (n = 318) to those who received only clopidogrel (n = 502) (Gaglia et al., 2010). It was observed that patients who received the combination therapy had more MACEs (death, target vessel revascularization and stent thrombosis) at one year, as compared to those treated only with clopidogrel (HR = 1.8, 95% CI 1.2–2.7, p = 0.01) (Gaglia et al., 2010). Other retrospective studies also showed that the administration of clopidogrel together with a PPI to patients after an acute MI and a coronary stent implantation increases the risk of recurrent MI within one year (Evanchan et al., 2010; Stockl et al., 2010).

In summary, the studies reviewed above indicate that the administration of a PPI (particularly omeprazole) with clopidogrel to patients after MI and a coronary stent implantation may reduce the therapeutic efficacy of clopidogrel and increase the rate of MACEs.

Studies that Do Not Support the Hypothesis that PPIs Reduce the Antiplatelet Activity of Clopidogrel

Despite the accumulating evidence indicating that PPIs reduce the antiplatelet activity of clopidogrel, contradicting findings have also been reported (Zairis et al., 2010). The recently published COGENT trial gave evidence against a possible interaction between PPIs and clopidogrel (Bhatt et al., 2010). It is the only prospective, randomized, double-blind, placebo-controlled study that examined whether concurrent treatment with clopidogrel and omeprazole reduces the therapeutic efficacy of clopidogrel. The study analyses included 3,761 patients who were treated with aspirin and clopidogrel and randomly assigned to receive either omeprazole (1,876 patients) or placebo (1,885 patients) (Bhatt et al., 2010). It was found that 1.1% of the patients who were treated with omeprazole had a GI event as compared to 2.9% of the patients who were given placebo (HR with omeprazole, 0.34, 95% CI, 0.18 to 0.63, p < 0.001). Moreover, the rate of overt upper GI bleeding was also reduced in the patients who were treated with omeprazole, as compared to placebo (HR with omeprazole, 0.13, 95% CI, 0.03 to 0.56, p = 0.001). Importantly, 4.9% of the patients who were treated with omeprazole had a cardiovascular event (death from cardiovascular causes, nonfatal MI, revascularization, or stroke), as compared to 5.7% of the patients who were given placebo (HR with omeprazole, 0.99, 95% CI, 0.68 to 1.44, p = 0.96). The authors concluded that the addition of omeprazole to aspirin and clopidogrel significantly reduced the rate of GI events (particularly upper GI bleeding) without increasing the rate of cardiovascular events (Bhatt et al., 2010).

Furthermore, observational studies have also questioned the interaction between PPIs and clopidogrel. It is important to emphasize that among the clinically used PPIs, it seems that only omeprazole significantly inhibits CYP2C19 and, thus, reduces the antiplatelet activity of clopidogrel (Sibbing et al., 2009; Siller-Matula et al., 2009). For instance, pantoprazole and esomeprazole did not have a negative effect on the antiplatelet action of clopidogrel (Sibbing et al., 2009; Siller-Matula et al., 2009). Thus, an important question remains to be answered: is the interaction with clopidogrel specific to one PPI (omeprazole) or it is a class effect? (Anderson, 1996; Roden & Stein, 2009; Sibbing et al., 2009; Siller-Matula et al., 2009). Another important argument is that most PPIs have a short half life (0.5 to two hours), suggesting that their inhibition of CYP2C19 is short, which enables metabolism of clopidogrel during later hours of the day, especially if these drugs are not given simultaneously (Juurlink, 2009).

In a large retrospective study, Rassen, Choudhry, Avorn, and Schneeweiss (2009) examined the effect of combining a PPI with clopidogrel on the incidence of MACEs among 18,565 patients who underwent a PCI or were hospitalized for ACS. The primary end point of the study was MI hospitalization or death. On a pooled basis, 2.6% of those who used a PPI had a MI hospitalization, as compared to 2.1% in PPI non-users; 1.5% died versus 0.9%; and 3.4% versus 3.1% underwent a revascularization, respectively. However, the propensity score-adjusted relative risk for the primary end point was 1.22 (95% CI 0.99–1.51, p = 0.31), and 1.22 (95% CI 0.95–1.57, p = 0.32) for MI hospitalization, 1.20 (95% CI 0.84–1.70, p = 0.36) for death, and, 0.97 (95% CI 0.79–1.21, P < 0.01) for revascularization (Rassen et al., 2009). The authors concluded that despite the

slightly increased risk (statistically non-significant) of MI hospitalization or death in PPI users, the results did not give conclusive evidence indicating that the interaction between clopidogrel and PPIs is of major clinical significance (Rassen et al., 2009).

Zairis et al. (2010) conducted a prospective study that included 588 patients who underwent a PCI plus coronary stent insertion; 340 patients were treated with clopidogrel alone and 248 received clopidogrel and omeprazole for at least one week. At one year of follow-up, the primary end point (the composite of cardiac death or rehospitalization for nonfatal MI) occurred in 58 (9.9%) patients, including 20 (3.4%) who died due to cardiac reasons and 38 (6.5%) who were rehospitalized because of a nonfatal MI. Patients were at similar risk of the primary composite end point, irrespective of whether omeprazole was (10%) or was not (9.7%) added to clopidogrel (HR 1.1, 95% CI 0.6-1.8, p=0.89). The authors suggested that treatment with omeprazole does not attenuate the clinical efficacy of clopidogrel during the first year after a PCI and coronary stenting (Zairis et al., 2010).

O'Donoghue et al. (2009) performed a sub-analysis of the TRITON-TIMI 38 trial in order to evaluate the risk associated with concomitant use of clopidogrel together with a PPI. In the TRITON-TIMI 38 trial, 13,608 patients with ACS were assigned to clopidogrel or prasugrel, of which, 33% (n=4529) also received a PPI. The primary end point of the trial was the composite of cardiovascular death, MI, or stroke. The sub-analysis revealed that there was no association between the use of a PPI with clopidogrel and the risk for the occurrence of the primary end point (adjusted HR 0.94, 95% CI 0.80–1.11) (O'Donoghue et al., 2009). Moreover, in a small study (n=201), which was part of the randomized BRIEF-PCI trial, Sedlak, Lam, Starovoytov, Fung, and Saw (2010) assessed the effect of combining a PPI together with clopidogrel on clopidogrel-induced platelet inhibition. The addition of a PPI to clopidogrel did not attenuate the antiplatelet activity of clopidogel. The authors also observed that pantoprazole (as compared to omeprazole, esomeprazole and rabeprazole) was associated with the lowest attenuation of clopidogrel platelet inhibition. However, the difference between the drugs did not reach a statistically significant difference (p=0.06) (Sedlak et al., 2010).

In summary, the studies cited above (particularly the COGENT trial) suggest that PPIs do not reduce the antiplatelet activity and therapeutic efficacy of clopidogrel.

Concluding Remarks and Recommendations

The evidence indicating that PPIs reduce the antiplatelet activity and effectiveness of clopidogrel was based mainly on data from retrospective observational studies. In most of the reviewed studies, the magnitude of association between simultaneous treatment with a PPI (together with clopidogrel) and a reduction in the therapeutic efficacy of clopidogrel is small to moderate (OR or HR less than 2). The results of the COGENT trial (a randomized, double-blind, placebo-controlled study) did not support the hypothesis that omeprazole reduces the therapeutic efficacy of clopidogrel (Bhatt et al., 2010). However, it is important to indicate that the COGNET trial was terminated prematurely and enrolled fewer patients than was originally planned, resulting in a low number (109) of cardiovascular events. In addition, because of the broad confidence limits for cardiovascular events (CI, 0.68 to 1.44; suggestive of a possible 44% increase in risk), the results of COGNET cannot unequivocally rule out a clinically meaningful increase in cardiovascular harm due to the use of omeprazole.

Consistent with the results of the COGNET trial, another recent study showed that the presence of CYP2C19 loss-of-function alleles did not affect the therapeutic efficacy of clopidogrel (as compared to placebo) (Pare et al., 2010). These results also suggest that alteration of CYP450 (particularly CYP2C19) function does not reduce the antiplatelet activity and effectiveness of clopidogrel.

The conflicting results, inconclusive evidence and the results of recent studies led the American College of Cardiology (ACC), the American College of Gastroenterology (ACG), and the American Heart Association (AHA) to publish an expert consensus document regarding the concomitant use of PPIs and thienopyridines (Abraham et al., 2010). The report concluded that despite the small magnitude association observed in positive observational studies, currently, there is no sufficient evidence to support the hypothesis that a significant clinical interaction between PPIs and thienopyridines (clopidogrel in particular) exists. The authors encouraged conduction of large, randomized, placebo-controlled trials to examine the causation issue (between the use of PPIs and attenuation of the therapeutic efficacy of thienopyridines) (Abraham et al., 2010). Moreover, the authors recommended the use of PPIs (or H_2 receptor blockers) in patients at high risk for upper GI bleeding. In patients at high risk for GI bleeding, PPIs are more efficient than H_2 blockers in reducing GI adverse events and bleeding (Abraham et al., 2010; Ng et al., 2010). On the other hand, a routine use of a PPI or an H_2 blocker is not recommended for patients at lower risk for GI bleeding (Abraham et al., 2010).

Following the publication of recent studies and independent of the consensus document (Abraham et al., 2010), the U.S. Food and Drug Administration

issued a revised recommendation regarding the possible interaction between PPIs and clopidogrel (U.S. Food and Drug Administration, 2010). The new recommendation suggests that the use of PPIs together with clopidogrel is not to be avoided and that only omeprazole may reduce the therapeutic efficacy of clopidogrel (U.S. Food and Drug Administration, 2010).

Several alternative approaches and treatment strategies have been suggested to overcome the possible interaction between PPIs and clopidogrel. For example, Juurlink (2009) suggested that H_2 blockers (such as ranitidine, famotedine and nizatidine) may be a sufficient treatment for a large number of low-risk patients. In addition, he suggested that among the currently available PPIs, pantoprazole may be the drug of choice. This recommendation is based on the emerging evidence indicating that pantoprazole does not reduce the antiplatelet activity of clopidogrel (Juurlink et al., 2009; Neubauer et al., 2010; Sibbing et al., 2009; Siller-Matula et al., 2009). However, it is important to mention that conflicting results have also been documented (Hall et al., 2009) and that there is no strong evidence (from randomized clinical trials) to support this recommendation (Abraham et al., 2010).

Moreover, it was suggested that when it is necessary to give a PPI with clopidogrel, these two drugs may be administered in separate hours of the day to minimize the interaction between them (Angiolillo et al., 2010; Juurlink, 2009; Laine & Hennekens, 2010). This suggestion is based on the fact that most PPIs have short half lives, ranging from 0.5 to two hours. Thus, taking clopidogrel four to six hours after a PPI should avoid the inhibition of its conversion to an active metabolite by CYP2C19. But, again, there is no clinical evidence to support this proposal. The results of the COGNET trial suggested that giving omeprazole and clopidogrel at the same time does not reduce the therapeutic efficacy of clopidogrel. The ACC/ACG/AHA consensus document did not give a conclusive recommendation in this regard, encouraging the conduction of randomized clinical trials to examine the utility of this strategy (Abraham et al., 2010).

Furthermore, another therapeutic alternative is to use prasugrel instead of clopidogrel, as a treatment for patients after a PCI and stent implantation. Prasugrel is a thienopyridine that was found to have a greater inhibition of platelet aggregation (Michelson et al., 2009; Wiviott et al., 2007). Importantly, the metabolism of prasugrel is not (mainly) carried out by CYP2C19 and a combination with a PPI does not seem to reduce its effectiveness (Mega et al., 2009b; Small et al., 2008). Therefore, prasugrel seems to be a good substitute for clopidogrel in patients requiring treatment with a PPI. Similarly, it is possible to use ticagrelor as a substitute for clopidogrel (Steg et al., 2010; Wallentin et al., 2009). Ticagrelor is an active parent drug (not a prodrug) that is a resevrsible $P2Y_{12}$ receptor antagonist, the metabolism of which produces an active metabolite (Capodano, Dharmashankar, & Angiolillo, 2010). Importantly, the presence of loss-of-function CYP450 alleles does not seem to alter the metabolism and efficacy of ticagrelor (Abraham et al., 2010). Ticagrelor was found more effective than clopidogrel in reducing MACEs in patients with ACS without increasing the rate of major bleeding (Steg et al., 2010; Wallentin et al., 2009). Taken together, these data suggest that prasugrel and ticagrelor are good substitutes for clopidogrel in patients who need a PPI to be administered with dual antiplatelet therapy.

Implications for Cardiovascular Nurses

Nurses should be aware of the possibility that concomitant administration of clopidogrel together with PPIs (particularly omeprazole) may attenuate the antiplatelet activity and therapeutic efficacy of clopidogrel. Therefore, patients who are administered both treatments must be closely monitored for signs and symptoms of recurrent acute coronary events such as stent thrombosis and MI. The signs and symptoms of acute ischemia may include one or more of the following: chest pain, cardiac arrhythmias, changes in blood pressure, sweating, dyspnea or/and shortness of breath, pulmonary congestion, pallor, weakness, GI disturbances (such as nausea, vomiting and abdominal discomfort), changes in electrocardiogram and alterations in cardiac biomarkers (e.g., elevated levels of troponin and creatine kinase-MB).

Alternatively, patients who are not given PPIs with clopidogrel may have an increased risk of dyspepsia and GI bleeding. In general, bleeding may be particularly significant in patients who are administered clopidogrel and aspirin. Other risk factors for bleeding are a history of GI bleeding; *Helicobacter pylori* infection; concurrent use of steroids, non-steroidal anti-inflammatory drugs, or anticoagulant drugs; and advanced age (Abraham et al., 2010). Measures to minimize the risk of bleeding may include careful observation of the limb into which the PCI sheath/catheter was inserted and appropriate bandaging/fixation of venous and arterial lines during hospitalization; monitoring of heart rate, blood pressure, hemoglobin levels and coagulation measurements; educating patients to use a soft tooth brush and a shaving machine (instead of a razor), report the occurrence of hematuria, dark stool or other signs of bleeding, and, avoid activities that may cause injury. Moreover, nurses need to address questions raised by patients regarding their treatment regimens and emphasize the importance of adherence to treatment and that discontinuation of clopidogrel (or aspirin) may increase the risk of recurrent cardiovascular events. ♥

About the Authors

Emilia Shmulevich, RN, Staff Nurse ICU, Department of Epidemiology, Ben Gurion University of the Negev and Cardiology Division, Soroka University Medical Centre, Beer-Sheva, Israel.

Michael Friger, PhD, MA, Professor and Head, Department of Epidemiology, Ben Gurion University of the Negev, Beer-Sheva, Israel.

Harel Gilutz, MD, Director ICU and Senior Lecturer Faculty of Health Sciences, Cardiololgy Division, Soroka University Medical Centre, Beer-Sheva, Israel and Ben Gurion University of the Negev.

Abed N. Azab, RN, PhD, Lecturer Faculty of Health Sciences and Staff Nurse ICU, School for Community Health Professions—Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel and Cardiology Division, Soroka University Medical Centre.

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Interior Health

Who we are

Be part of an exciting and dramatic expansion of Cardiac Services in British Columbia. As the only service of its kind between Vancouver and Calgary, our new program will provide residents of the British Columbia interior with the cardiac care they need, closer to home.

Phase One of the Cardiac Services expansion was the launch of PCI services at Kelowna General Hospital in November 2009.

We are now recruiting for Phase Two of our expansion, which is the introduction of open heart surgery in December 2012. We are building a team that will ensure the highest standards of patient and family care for cardiac services throughout our region. Come and join our team.

To learn more about the Kelowna General Hospital expansion visit www.buildingpatientcare.ca.

Exciting Cardiac RN Opportunities in the Beautiful Interior of BC

Kelowna General Hospital

We currently have full and part-time positions available for Registered Nurses in the following units:

Cardiac Surgery Intensive Care Unit (CSICU) Competition #338852

Cardiac Surgery In-Patient Unit Competition #342445

Cardiac OR Competition #319778

We have what you want:

- competitive wage
- excellent employee benefits (medical, dental, life & disability insurance) – premiums are 100% paid by Interior Health
- pension plan
- relocation assistance program
- professional development & educational leave
- a larger than life landscape & four seasons playground & a pace of life that is simply...better!
- four weeks of vacation

To apply for any of these positions, please visit our website at www.roomtogrowbc.ca and apply to the Competition numbers noted above or e-mail **wendy.howes@interiorhealth.ca**.

Room to Grow... in British Columbia

www.roomtogrowbc.ca