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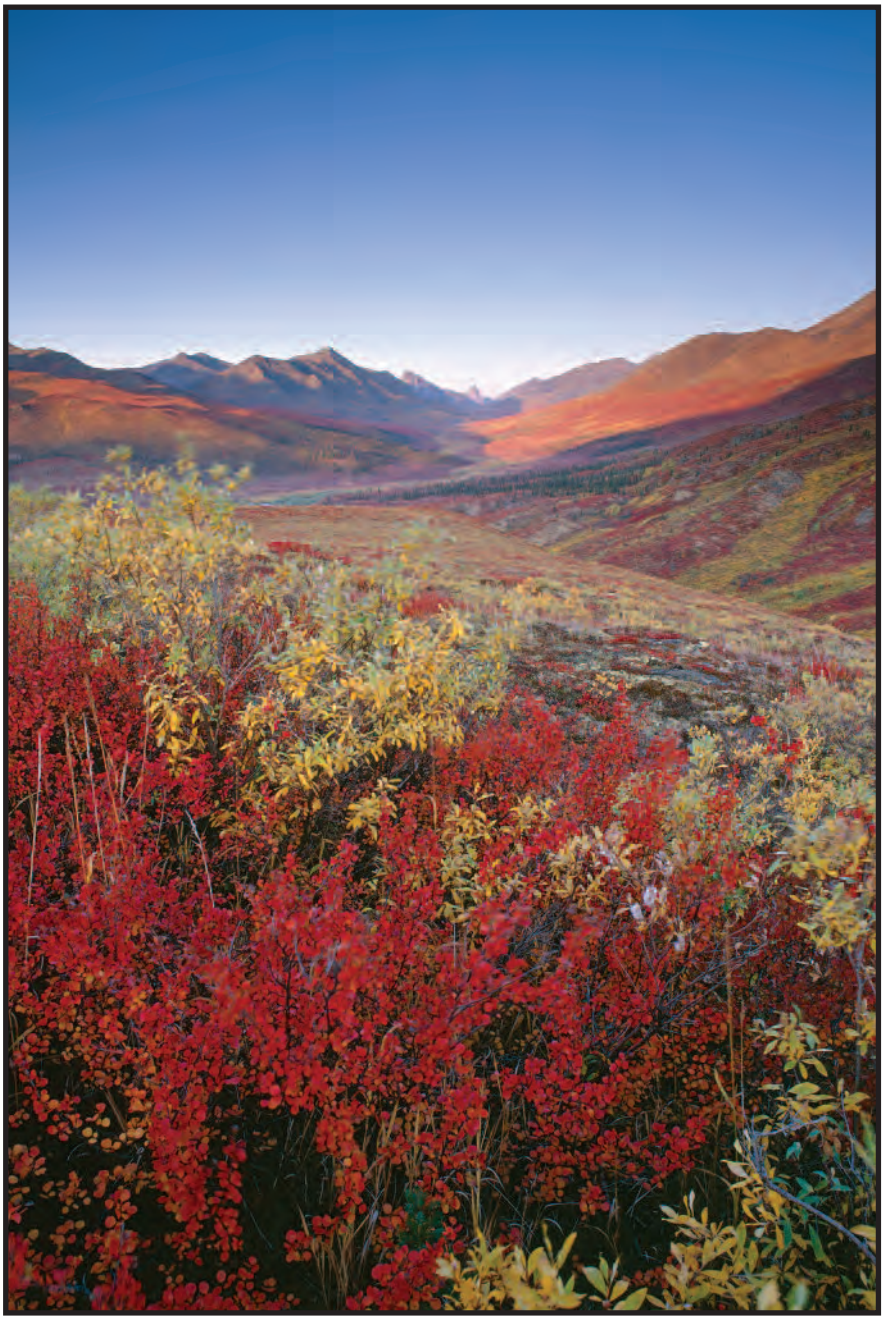
Canadian Journal of General Internal Medicine

LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE



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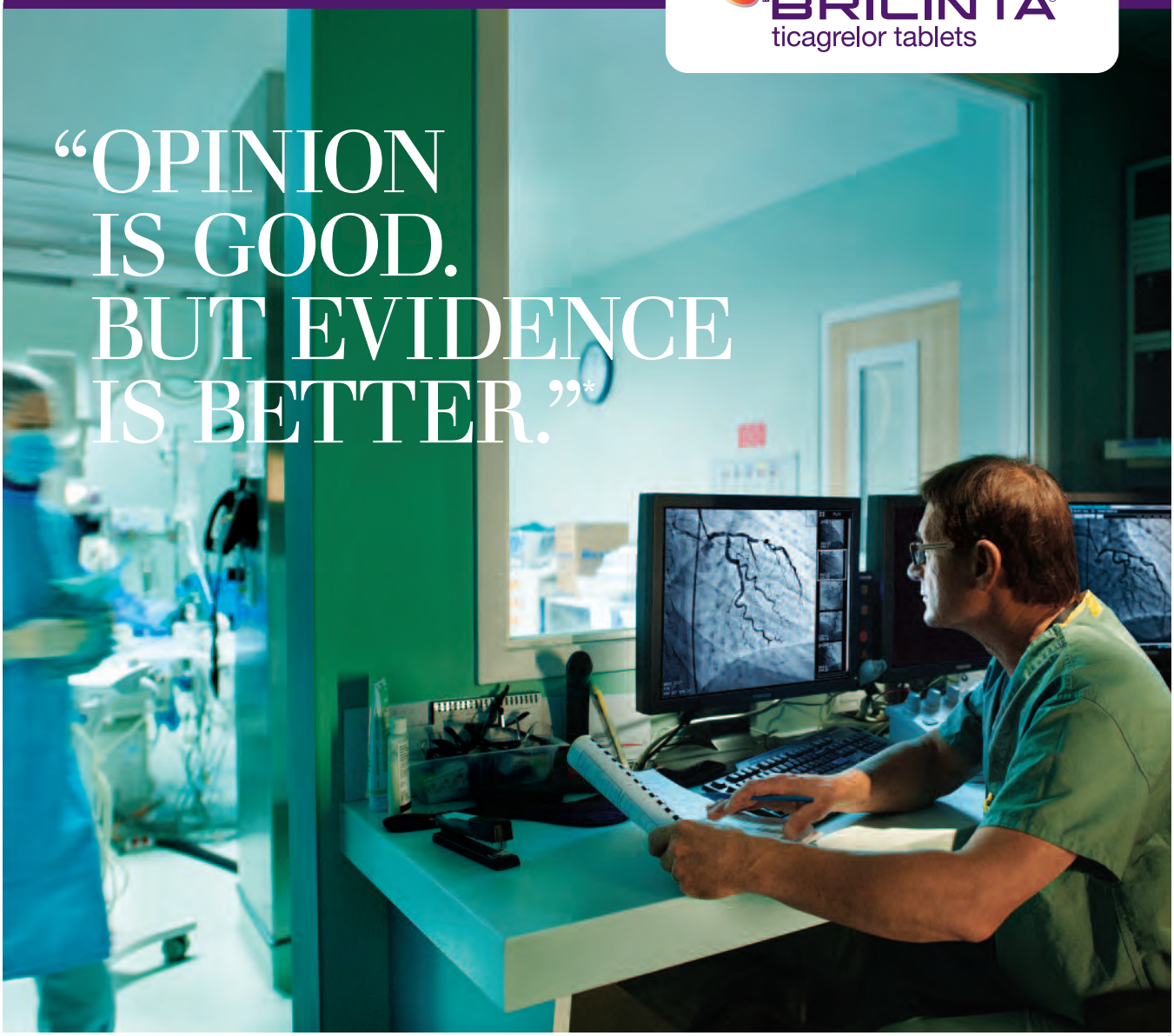

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Reference: 1. BRILINTA® Product Monograph. AstraZeneca Canada Inc. May 26, 2011.

*Fictitious quote. May not be representative of all healthcare professionals.

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See prescribing summary on page 28

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We acknowledge the financial support of the Government of Canada through the Canada Periodical Fund of the Department of Canadian Heritage.

ABOUT THE COVER

Photographer James R. Page rose from his frost-covered tent before dawn in early September to capture this classic autumn view of the North Klondike Valley and distant Tombstone Mountains, north of Dawson City, Yukon. Page is the author of *Prairie: A Natural History*, published by Greystone Books, Vancouver, British Columbia. He currently lives in Val Marie, Saskatchewan, where he runs photo workshops in and around Grasslands National Park. See more of his photos at www.flickr.com/photos/pageworld, or contact him at pageworld@sasktel.net.

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Canadian Society of Internal Medicine Osler Awards 2011

The prestigious Osler Award is the highest honour that the CSIM bestows on individuals in recognition of extraordinary professional contributions and achievements over the course of a career. It is presented annually to physicians who demonstrate excellence in achievement in the field of general internal medicine, in clinical practice, research, medical education, or specialty development.

Dr. Barrie Phillips, Community Internist, Terrace, British Columbia

Dr. Phillips trained at Queen's and Vancouver (IM – 1972). He has practised at Mill Memorial Hospital in Terrace since that time. He has served the communities of Terrace, Smithers, and Kitimat, largely as a solo practitioner until 1995. He was a pioneer of cardiovascular techniques in rural British Columbia. He enjoys teaching and is a recipient of the Silver Medal of the BCMA.

Dr. Belluru Satyanarayana, Community Internist, Bathurst, New Brunswick

Dr. Satyanarayana graduated from Mysore University, India, and gained nephrology certification in Canada in 1971. He has served on many hospital committees and acted as chief of medicine at Chaleur Regional Hospital for over 35 years. Often the lone internist, he has provided quality and seamless care in rural New Brunswick, and has been inspired others through his dedication and example.

Dr. Danny Panisko, University Internist, Toronto, Ontario

Dr. Panisko has been recognized as an outstanding teacher for 20 years, resulting in many awards and honours. He is the director of the Master Teaching Program for the Department of Medicine at the University of Toronto, and has led several initiatives in advanced learning. He has impacted the lives of many students and teachers alike.

Dr. Mark Whalen, Community Internist, Campbellton, New Brunswick

Dr. Whalen graduated from University of Moncton and Sherbrooke, and has practised in Campbellton for over 25 years. He is currently GIM and CCU director at Campbellton Regional hospital: he established their echo service in 1986, then TEE and stress echo modalities. He started their first Pacemaker and ICD clinic, and more recently their Cardiac Rehab and HF clinics.
He is recognized as a superb clinician and community medical leader.

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Climate Change and the Clinician

Michael Irvine MD

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Michael Irvine is an internist working in Prince County Hospital, Summerside, Prince Edward Island. Correspondence may be directed to irvinemichael1@gmail.com.

Our ancestral home, this familiar blue and green orb with a white cap glistening into space, is changing in ways and at speeds never before witnessed. As our planet warms, acidifies, melts, inundates, and desiccates, we are staring down extinction: likely of our civilization, possibly of our species.

There are many reasons why physicians must act to mitigate the accelerating degradation of our planet. Man-made global warming has expanded the range of many disease vectors. This process has already caused suffering and loss of life in less-developed regions. With two out of three humans expected to face severe water shortages by 2025, and a dying acidified ocean expected by late century, our ability to provide quality health care in an already resource-constrained environment will certainly be impacted by the mass migrations, hunger, and political instability that are expected before century's end under a business-as-usual carbon emissions scenario.[1] These are compelling enough reasons to act. At bottom, what should motivate and unite the medical profession to take action against climate change is medical ethics.

In this century, medical ethics must include an obligation to future generations. We as a profession are called upon to set an example of intergenerational stewardship. This calls for altruism (those future generations will not return the favour), long-term thinking, and the ability to recognize an emergency. All are skills exercised daily by clinicians. We in the rich industrialized Minority World also have an obligation to those in the Majority World who contributed least to the problem of climate change but suffer the worst consequences.

Doubt Is Our Product: The Denial Industry

Awareness of the unfolding climate crisis has grown over the past 50 years, gaining momentum with the first congressional hearings on climate change in 1981 and the founding of the Intergovernmental Panel on Climate Change (IPCC) in 1988. A small but vocal culture of climate change deniers has defied the scientific consensus from the outset. Funded and backed by fossil fuel companies and largely organized into "think tanks" serving as corporate fronts, these voices, though increasingly marginalized, have grown louder as fossil fuel revenues have skyrocketed (Table 1). That many of these climate change denial groups have also received tobacco funding in the past and hire recycled tobacco advocates is no coincidence since tobacco and fossil fuels are dangerous, addictive, and highly lucrative products that need to be regulated and curtailed for the good of society. In the words of a leaked tobacco company memo, "Doubt is our product," referring to the campaign to deny the health effects of smoking.[2] Oil companies have followed the same script, selling doubt about climate change.

Few climate change deniers still argue that the planet is not warming: the temperature record is incontrovertible. Many maintain that the observed warming is due to increased solar activity, despite the fact that the most dramatic warming of the past decade coincided with a solar minimum, and solar variance alone would have predicted cooling over the past 50 years.[3,4]

Just the Facts: The IPCC

The work of IPCC, the Nobel Prize–winning consortium of the world's foremost climate scientists that reports every 5 years, has been described as the most comprehensive scientific study

Table 1. Tobacco Advocacy/Climate Change Denial Think Tanks and Their Funding

Institute	Tobacco Funding	Oil Company Funding
Independent Institute	Philip Morris	Exxon Mobil
Heritage Foundation	Philip Morris	Chevron Texaco
Reason Foundation	Philip Morris	Chevron Texaco, Exxon Mobil, Shell
Competitive Enterprise Institute	Philip Morris	Amoco, Texaco
Heartland Institute	Philip Morris	Exxon Mobil
American Enterprise Institute	Philip Morris	Exxon Mobil
Cato Institute	RJ Reynolds	Exxon Mobil
Fraser Institute	Rothman's, Philip Morris	Exxon Mobil

Source: Data from www.sourcewatch.org/index.

Table 2. Key Observations from the IPCC Fourth Assessment Report 2007

Parameter	Observation
Mean global temperature rise	0.7°C since 1900
Sea-level rise	3 mm/y since 1990; 1.7 m since 1900
Temperature records (year)	2005 warmest ever; 2010 tied
Atmospheric CO_2 rise	100 ppm since pre-industrial era; currently rising 2 ppm/y
Extreme weather events	3- to 4-fold increase in category 5 hurricanes in past decade

Source: Intergovernmental Panel on Climate Change.[4]

ever undertaken by humanity. IPCC has earned a reputation for rigorous methodology and conservative predictions that in retrospect have consistently underestimated the severity of climate change. When IPCC sounds alarmed, we *should all* be alarmed. The 2007 IPCC report is a must-read.[4] The report is divided into observations of past and current climate change, and projections for the future. The key observations are summarized in Table 2.

The IPCC's projections include a sea-level rise of 0.6 m by the end of the century, though updated estimates call for 1.6 m. Mean global temperature is projected to rise 0.2°C per decade, with enormous variance depending on emissions scenarios.

What does this portend for our future? Stronger hurricanes, more lethal droughts, melting of the remaining glaciers, a vanishing Arctic ice cap, flooding of coastal cities – in other words, more of what we are already seeing. But this barely scratches the surface. The rest of the story is beneath the ocean.

Sour Oceans and Melting Ice

Of the estimated 500 gigatons of carbon released into the atmosphere since the start of the Industrial Revolution, roughly 40% has dissolved in the ocean as CO_2. Some has been taken up by soil and vegetation, and the remainder has entered the atmosphere, increasing atmospheric CO_2 from 280 parts per million (ppm) to the current value of 390 ppm. Ocean uptake of CO_2 has caused the ocean pH to drop by 0.1 units from its long-preserved value of 8.2 to 8.1, a staggering 30% increase in ocean acidity. The ocean is the extracellular fluid of unicellular marine organisms that carry out 75% of the photosynthesis on earth and forms the basis of the global food chain atop which we sit. A pH change of this magnitude affects the formation of calcium carbonate shells by marine organisms from microscopic algae to shellfish, and is occurring at a rate that overwhelms adaptation. Ocean acidification, along with ocean warming, is also lethal for the coral reefs that shelter at least a million species of fish and whose demise is predicted this century.[5]

As glaciers and ice sheets melt and the warming ocean's expand, sea level has risen 1.7 m since 1900. The rate was 1.7 mm/y until about 1990 and is now 3 mm annually. (For each metre of sea-level rise, expect 50–100 m of horizontal shoreline loss.) With the behaviour of large ice sheets being unpredictable, no one is predicting when the Greenland or Antarctic ice sheets will break up; but when they do, sea levels will rise 7 m and 75 m, respectively. In the case of the Greenland ice sheet, breakup this century is possible.

Déjà Vu in Reverse

The earth has been down this road before. Fifty million years ago, global temperature rose to a breathtaking 12°C warmer than today due to natural causes that probably included a lot of tectonic activity (Figure 1). This was accompanied by a gradual rise in atmospheric CO_2, albeit one twenty-thousandth the current rate of rise.[4] This has been termed the Paleocene-Eocene thermal maximum (PETM), and the final phase of dramatic warming was triggered by a 3,000-gigaton discharge of carbon, very likely a warming-induced release of methane from methane hydrate crystals stored on shallow ocean floors. These fragile lattices of ice and methane have been replenished over the long cooling trend that followed the PETM to the tune of 5,000 gigatons waiting to be released into the atmosphere by warming. With the current 2 ppm annual rise of atmospheric CO_2 and unprecedented rate of warming, we risk playing this scenario in reverse.

Hot, Wet, and Hungry

Long before the waves of a dead acidified ocean lap at our heels as we flee for higher ground, man-made global warming will exacerbate an existing problem: global hunger. Global per capita grain production peaked in 1985, and in roughly half of the past 10 years, annual grain consumption has exceeded production.[6] As oceans die, fisheries collapse. Rivers fed by melting glaciers will dry up as the arid brown belts north and south of the Equator migrate pole-ward at a rate of 50 km per decade and fossil fuel-based fertilizers dwindle with oil supplies. The resources for a second Green Revolution no longer exist.

The Path Ahead: Global Action

Concerted global action is needed now. From the ongoing and often-heated debate, some points of consensus may be coalescing:

- Coal emissions must be phased out rapidly. We are not

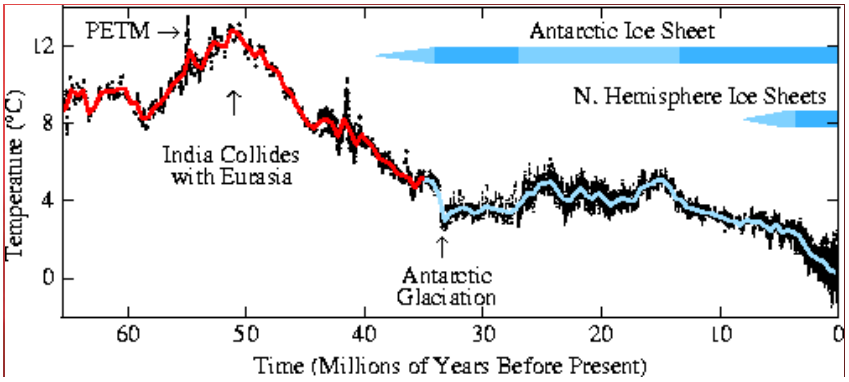

Figure 1. The Paleocene-Eocene thermal maximum (PETM) and the long cooling trend that followed.

Source: Reprinted with permission from Dr. Makiko Sato, from Hansen J. Storms of my grandchildren (Figure 18, Chapter 8). New York: Columbia University; www.columbia.edu/~mhs119/Storms.

all going to stop driving and flying tomorrow, and coal, responsible for 40% of CO_2 emissions, is the only major carbon source for which renewable alternatives could be implemented in a reasonable time frame.

- Unconventional oil sources (tar sands and oil shale) and most of the remaining fossil fuels must be left in the ground. Burning all remaining fossil fuels virtually guarantees another PETM-like catastrophic warming event.
- Fossil fuel subsidies ($1.4 billion a year in Canada alone) must end. "Big Oil" doesn't need the cash.
- Some form of carbon tax must be implemented to reflect the true social cost of fossil fuel burning and to incentivize development of renewable energy. British Columbia has already done this, and we need to follow its example.
- There must be massive investment in renewable energy.

Sound expensive? IPCC estimates that the climate could be stabilized at a cost of 1% of global gross domestic product (GDP).[7] By contrast, the Allied war effort that defeated global fascism in World War II cost 15% of the GDP. The Allies emerged from that struggle more prosperous than ever, went on to build the affluent society we live in, and put man on the moon for an encore.

What can we do as individuals? Personal carbon footprint reduction – too large a subject to cover here – is necessary but not sufficient to avert climate catastrophe. We need to change those light bulbs and walk or bike to work, but we should not imagine that these actions alone will save the planet.

We as physicians should inform ourselves and others. Above all, we need to embrace non-partisan political activism, a task for which, as I have argued above, our training has groomed us. As Margaret Mead said: "Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has." Without citizen activism, the slave trade would still be thriving and women would not vote. In my home province of Prince Edward Island, 90% of practising physicians signed a petition that in July 2011 was presented to the premier indicating our concern about the climate crisis and calling upon the government to take definitive action. This was a small symbolic step, and a starting point.

Our species faced a crisis of similar magnitude 70,000 years ago, in the middle of the last Ice Age. A massive volcanic eruption in what is now Indonesia plunged the earth into a 1,000-year cold snap, causing severe drought in Africa. The human population may have been reduced to as few as 2,000 drought survivors. This genetic bottleneck explains why we humans are an unusually homogeneous group with a fraction of the genetic variability seen in other species. How did we survive that near-extinction crisis? We moved on, out of our African homeland, and populated the rest of the planet. The great migration of 60,000–70,000 years ago saved our species.

That strategy will not work again because there are no nearby habitable planets awaiting us. It is time stop behaving as if there were.

References

1. Epstein P, Ferber D. Changing Planet, Changing Health. Los Angeles (CA): University of California Press; 2011.
2. University of California, San Francisco. Legacy tobacco documents library. San Francisco (CA): The University; http//legacy.library.ucsf.edu. Accessed October 31, 2011.
3. Hansen J. Storms of My Grandchildren. New York: Bloomsbury; 2009.
4. Intergovernmental Panel on Climate Change. IPCC fourth assessment report. Geneva, Switzerland: The Panel, 2007; http://www.ipcc.ch/publications_and_data/ar4/syr/en/contents.html. Accessed October 31, 2011.
5. Kolbert E. The darkening sea. The New Yorker. 2006 Nov 20.
6. Dyer G. Climate Wars. Toronto (ON): Vintage Canada; 2008.
7. Archer D, Rahmstorf S. The Climate Crisis. Cambridge (MA): Cambridge University Press; 2010.

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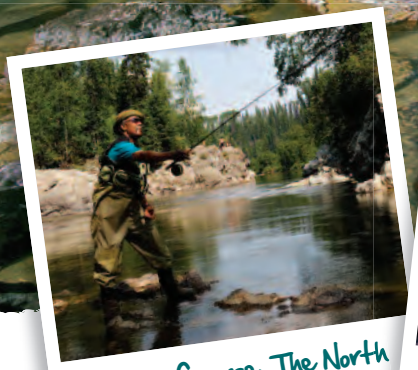
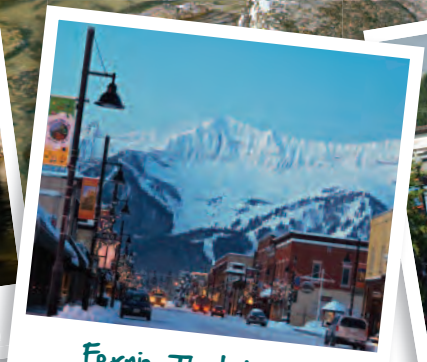


Prince George, The North



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Airway Management, A Primer for the Internist: Part 1

Peter G. Brindley MD, Stuart F. Reynolds MD, Michael Murphy MD

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"Managing an airway" means different things to different practitioners. However, it is widely understood to mean ensuring an open breathing pathway (a.k.a. airway patency), protecting the lungs from aspiration (a.k.a. airway protection), and ensuring both oxygen delivery and carbon dioxide removal (a.k.a. oxygenation and ventilation). It should be no surprise that improper airway management is a significant cause of in-patient morbidity and mortality. Competence in this area should be considered an important skill. This simple primer will not create experts. However, we do offer practical tips to temporize, triage, and tackle the patient who has airway compromise.

There is more to airway management than just intubation. In this article, we cover the rudiments of positioning, airway adjuncts and bag-mask ventilation (BMV), and airway assessment. The supplemental topics of laryngoscopy, endotracheal intubation, extra-glottic devices, airway pharmacology, and post-intubation care will be covered in a later article (part 2) in this journal. As with all medical topics, there is no substitute for "hands-on" experience, ongoing practice, and well-honed team management skills.

Airway Positioning: Sniff the Air, but Understand What It Means

The optimal head position for airway alignment (and attempted intubation) has been traditionally described as the "sniffing position." Practitioners should beware that many novices fail to understand what is implied. It describes flexion of the lower cervical spine, extension of the upper cervical spine, and positioning the tragus of the ear at least level with, or in front of, the sternomanubrial junction. This position may not be achievable all patients, for example, those with neck trauma. Fortunately, simple neck extension alone may be effective. Of note, recumbency may be also difficult in many critically ill patients (due to pulmonary edema or ascites). In these cases, patients can be positioned in a semi-Fowler's or reverse-Trendelenberg position. The three aspects of airway positioning are especially important in obese patients, where the optimal position can be attained by using blankets, towels, or other devices. This can also be achieved by reconfiguring the normally flat bed (or operating room table) with flexion at the trunk-thigh hinge and raising of the back (trunk). Regardless, the importance of proper positioning explains why the impulse to remove pillows is inappropriate in adult patients. If pillows are removed due to concerns of excessive head-flexion, the use of rolled-up towels under the shoulder and occiput is recommended. Airway experts also recommend that unless clinicians intubate regularly (the exact number is unclear), they should defer to others if possible. As such, it seems prudent that internists focus on pre-oxygenation, BMV, and maintenance of airway patency.

Airway Patency: Keep Your Options "Open"

Patients may have an obstructed airway due to the presence of foreign bodies, infections, blood, vomit, trauma, or secretions. However, the medical patient is particularly at risk of closure of the pharynx due to inadequate tone and redundant tissue. Cautious efforts should be made to clear the airway, but deep suctioning can cause laryngospasm and precipitate obstruction. If the airway remains compromised, a head-tilt-chin-lift or jaw-thrust maneuver is recommended (Figure 1). If the patient has spinal pathology, then the chin-lift should be avoided but the jaw-thrust can still be used to open the airway. These manoeuvres work by increasing the distance between the soft palate and posterior tongue – the most common site of obstruction.

If the airway remains obstructed despite a clear oropharyngeal space and a head-tilt-chin-lift/jaw-thrust maneuver, then the obstruction is likely more distal. It may also be the result of laryngospasm. This usually responds to gentle suctioning, cessation of overt airway stimulation, airway repositioning (again by the chin-lift or jaw-thrust), and gentle but persistent positive pressure by BMV. Oropharyngeal airways (OPAs) and nasopharyngeal airways (NPAs) can also be life-saving devices in order to maintain a patent airway. However, placing an OPA can be a noxious stimulus. It should therefore be cautiously placed, especially in lightly sedated patients. NPAs are somewhat better tolerated, but topicalization of the nasal

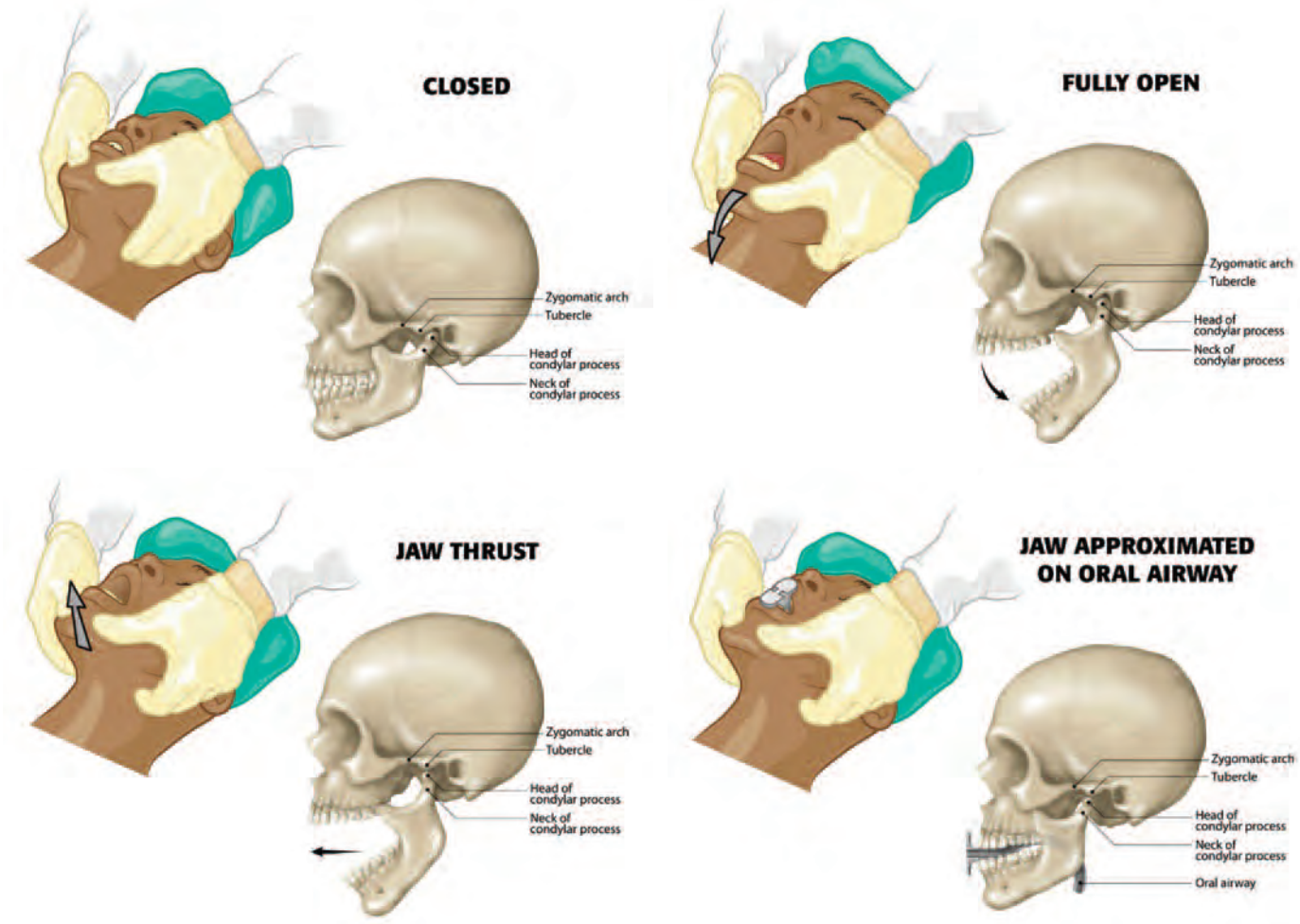

Figure 1. The anatomy of an optimum jaw thrust: disengaging the temporomandibular joint and "translating" the mandible forward. The tongue is attached to the mentum and the epiglottis to the tongue (via the hyoid), and both move forward with a jaw thrust.

mucosa with local anesthetic and vasoconstrictors is recommended in awake patients. The NPA is contraindicated in basal skull fractures or severe facial trauma. In rare instances, both an OPA and NPA may be required. Regardless, they should be sized to ensure that the distal end rests beyond the base of tongue, just above the epiglottis. If they are too long, they can cause laryngospasm; too short, and they are ineffective. Most clinicians size the OPA against the cheek, from the corner of the lips to either the angle of mandible or tragus of the ear. Alternatively, most adult females take an 8 cm and most adult males a 9 or 10 cm OPA. The OPA should be inserted with its concave side cephaled (i.e., inverted) and until resistance is felt. It is then rotated 180° (the concavity now faces caudal) until fully inserted to the lips. This technique minimizes the posterior displacement of the tongue, which could aggravate the obstruction. Adult NPAs are sized by internal diameter, with small, medium, and large corresponding to 6, 7, and 8 mm (6 mm for an average female, 7 mm for an average male).

Oxygenation and BMV: Vital Skills to Maintain Vital Signs

In the critically ill patient, oxygenation is achieved passively by enriching the oxygen content of inspired gas via nasal prongs or a face mask, or actively via BMV (with or without a positive end-expiratory pressure [PEEP] valve). It can also be achieved by employing a non-invasive positive pressure circuit (e.g., continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPaP]). When the goal is to attempt active airway management, high oxygen concentrations are ideally delivered for several minutes in order to displace alveolar nitrogen and create an oxygen reservoir (de-nitrogenation or pre-oxygenation). Though patients with severe chronic obstructive pulmonary disease (type II respiratory failure) may rely upon a hypoxemic drive, when facing possible respiratory arrest, it is more important to maintain an oxygen saturation of at least 90%. Therefore, oxygenation takes precedence and the critically ill patient should receive 100% oxygen. Clinicians

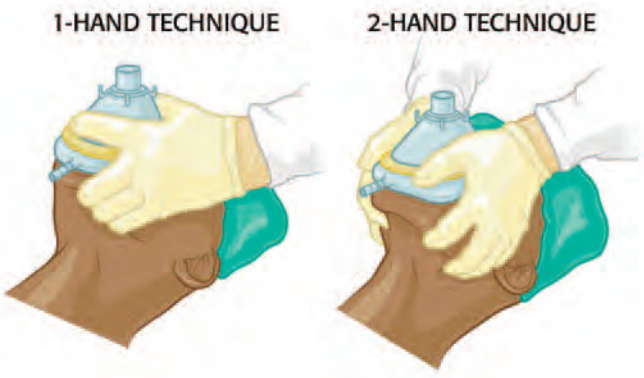

Figure 2. During bag-mask ventilation, the mask's lower border is applied to the groove between lower lip and chin, and the upper edge is placed on the nasal bridge.

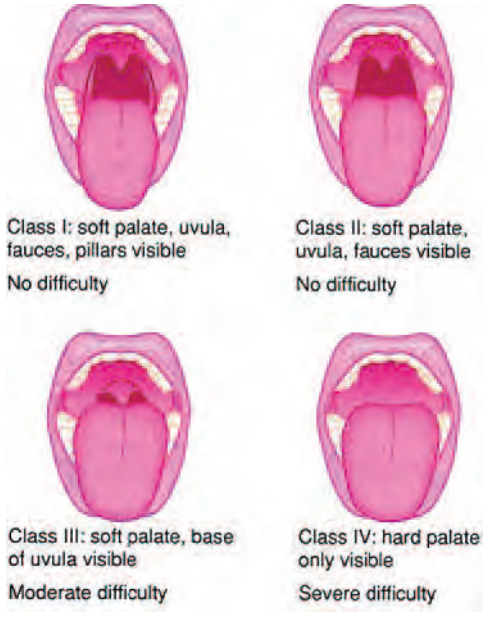

Figure 3. Mallampati classifications.

Source: Reproduced with permission from Hung O, Murphy MF. Management of the Difficult and Failed Airway, 2nd edition. McGraw-Hill; 2012.

should be cognizant of the potential for human errors: (1) mistakenly attaching the oxygen tubing to the neighboring medical air outlet; (2) attaching same to the suction outlet; (3) appropriately attaching to the oxygen outlet but without the oxygen flow-meter turned on; (4) letting the oxygen tubing sit on the floor or attached to an empty oxygen tank; and (5) causing inadequate oxygen flow as indicated by failure of the reservoir bag to inflate. Oxygenation (a.k.a. de-nitrogenation) is particularly important where patients have low functional residual capacity due to obesity, abdominal surgery, or lung de-recruitment.

BMV is a difficult skill. It requires a mask seal, airway opening, and assessment of oxygenation and ventilation. In order to size the mask, its lower border is applied to the groove between lower lip and chin, and the upper edge is placed on the nasal bridge (Figure 2). The clinician's thumb and index finger apply pressure to achieve a seal but without displacing the mandible posteriorly as this can cause airway obstruction. In contrast, the mandible should be lifted to meet and seal with the mask. This is done using the ring and long fingers to grasp the inferior surface of the mandible, and the fifth finger to exert upward pressure under the angle of the mandible. These fingers apply counter-pressure to the thumb and index finger. Of note, fingers should not be placed under the chin as this can compress the submandibular space. The clinician's opposite hand gently squeezes the BMV's self-inflating bag either upon inspiration (to assist the still breathing patient) or at a rate of approximately 10–15 breathes per minute and approximately 500 mL per breath. The clinician should then look, listen, and feel to identify a myriad of signs including (but not limited to) chest expansion and improving saturation and minimal air leak. BMV requires ongoing small adjustments to the position of the mask, the clinician's hand, and the patient's head. This requires experience and diligence and should therefore not be relegated to a less-skilled member of the team. It may also require more than one person, namely one to bag and another to maintain a tight seal and adequate lift on the mandible (with one or two hands). The need for BMV also means that the physician should be planning for transfer to the intensive care unit (ICU) and probable intubation.

Airway Assessment: Treat All Airways as If They Might Be Difficult (Because They Can Be!)

There are clues as to which patients will likely be more difficult to manage. When time permits, a rudimentary airway assessment is advised. The caveat is that these models were typically developed for patients in the operating room, and have not been widely validated in the ward, ICU, or emergency room. Independent predictors of difficult mask ventilation include obesity, a beard, a Mallampati score of III or IV (see below; Figure 3), age >57 years, limited jaw protrusion, and a history of snoring. The independent predictors of impossible mask ventilation are a history of neck irradiation or sleep apnea and either a beard or Mallampati III/IV visualization. Risk factors for the combination of difficult or impossible mask ventilation and difficult intubation include Mallampatti III/IV, an abnormal cervical spine, a thick obese neck, a thyromental distance <6 cm, a mouth opening of <3 cm, limited mandibular

protrusion, snoring, sleep apnea, and obesity. Additional risk factors for a difficult airway include limitations in spinal movement (e.g., rheumatoid or osteoarthritis, spondyloarthropathies, trauma, even severe diabetes) and macroglossia (e.g., in hypothyroidsim and Down syndrome).

While the Mallampati classification is useful in evaluating for difficult airway management, it was intended for patients undergoing elective intubation. Regardless, it consists of instructing a patient to sit upright and protrude his or her own tongue. The physician estimates how much of the posterior pharynx and uvula can be visualized using a four-point system, from best (I) to worst (IV). Reasonable correlation exists between classes I and II and easy direct laryngoscopy. Similarly, classes III and IV suggest difficulty. Obviously, though, this is of limited use for emergency intubations or for the unco-operative or comatose patient. However, in preparation for intubation, any clinician can rapidly assess mouth opening (three fingerbreadths suggests adequate room for insertion and rotation of the laryngoscope blade) and thyromental distance (three finger breadths suggests adequate space for the laryngoscope blade to compress the tongue). The clinician can also perform a mandibular protrusion test (the conscious patient has the ability to protrude the lower teeth at least 1 cm, or to cover the upper lip with the lower incisors). Regardless, resuscitation should always be a team pursuit. (There really is no "I" in ICU!) As such, it seems appropriate to end with this advice: get help, and get help early.

Recommended Sources for Additional Reading

Brindley PG, Simmonds MR, Needham CJ, Simmonds KA. Teaching airway management to novices: a simulator manikin study comparing the 'sniffing position' and 'win with the chin' analogies. BJA 2010;104(4):496–500.

Finucane BT, Tsui BCH, Santora AH. Principles of Airway Management, 4th edition. New York: Springer Press; 2011.

Hung O, Murphy MF. Management of the Difficult and Failed Airway. New York: McGraw Medical; 2008.

Kovacs G, Law JA. Airway management in emergencies. New York: McGraw Medical; 2008.

Neilipovitz D. Acute resuscitation and crisis management. Ottawa (ON): University of Ottawa Press; 2005.

Atypical Neuroleptic Malignant Syndrome Associated with Atypical Antipsychotics

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Case

A 58-year-old man with bipolar disorder presented with a 6-day history of confusion, delirium, and unsteady gait. His psychotropic medications included divalproex 500 mg qam and 750 mg qpm, lamotrigine 150 mg bid, quetiapine 300 mg qhs, and venlafaxine 150 mg od. Within 5 days of taking newly prescribed ziprasidone 40 mg bid and benztropine 1 mg bid for tremors, his wife noted unusual behaviour, increased tremulousness, diaphoresis, and falls.

His vital signs were normal: in particular, he was afebrile. He was alert but disoriented to time, place, and person. He was tremulous, and reflexes could not be assessed. He had increased tone in his upper and lower extremities. There was decreased sensation at the fingertips and mid-foot bilaterally, and decreased temperature and proprioception in both feet. A Romberg test was positive, and he had a wide-based ataxic gait. He did not have dysmetria. He had psychomotor retardation despite a euthymic affect, and decreased concentration and memory, but no suicidal or homicidal ideation. His speech was dysarthric and paraphasic, and he displayed incoherent thought processes, as well as confusion and alterations in level of consciousness during his hospital stay. He had visual hallucinations, was physically and verbally aggressive toward hospital staff, and had poor insight and judgement. The remainder of physical examination was unremarkable.

Pertinent laboratory findings included a mild normocytic anemia, with normal serum chemistry and normal levels for B_{12} and folate, thyroid-stimulating hormone (TSH), A1c, and valproic acid. His urinalysis was normal, and his toxicology screen was negative. His C-reactive protein (CRP) was 12.5 mg/L, erythrocyte sedimentation rate (ESR) was 56 mm/h, and he had an elevated creatine kinase (CK) of 758 U/L, peaking at 3,750 U/L. Computed tomography (CT) of the head without contrast was normal. An electroencephalogram (EEG) showed very mild generalized slow-wave excess consistent with medication effect or a toxic metabolic encephalopathy. No epileptiform potentials were seen.

Table 1. Differential Diagnosis

Neuroleptic malignant syndrome
Serotonin syndrome
Anticholinergic delirium
Seizure
Stroke
Heat stroke
Infection
Catatonia

After ruling out other differential diagnoses (Table 1), our patient was treated for presumed neuroleptic malignant syndrome (NMS). His antipsychotic medications were discontinued. He was rehydrated with intravenous fluids and treated with bromocriptine, clonazepam, lorazepam, and supportive care. Over the following 7 days, he made a full recovery.

Discussion

NMS is a rare but potentially fatal complication of treatment with antipsychotic medication, first characterized by Delay and colleagues in 1968. Although most cases involve typical antipsychotics, the syndrome has also been reported with other drugs, including atypical antipsychotics, lithium, antidepressants of various classes, and metoclopramide. It has also been seen following a sudden withdrawal of dopamine agonists in Parkinson's disease.[1]

According to the criteria in *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV),[2] NMS is typically characterized by the development of severe muscle rigidity and hyperthermia, and accompanied by two (or more) of the following symptoms: diaphoresis, dysphasia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, alterations in blood pressure, leukocytosis, and laboratory evidence of muscle injury (e.g., elevated CK).

Diagnostic criteria for NMS remain a controversial area, and various criteria have been proposed (Table 2),[2–7] highlighting

Table 2. Proposed Criteria for Diagnosing Neuroleptic Malignant Syndrome

Muscle rigidity
Hyperthermia
Diaphoresis
Dysphagia
Tremor
Incontinence
Changes in level of consciousness
Mutism
Tachycardia
Alterations in blood pressure
Leukocytosis
Elevated creatine kinase

Sources: Data from American Psychiatric Association,[2] Pope et al.,[3] Caroff et al.,[4] Levenson,[5] Addonizio et al.,[6] and Adityanjee.[7]

the variability of NMS in its clinical presentation. *Fever and muscle rigidity* are characterized as core criteria, but Levenson[5] proposes that NMS can be diagnosed in the absence of one of these signs if other manifestations are consistent with NMS. *Autonomic signs* are viewed as an essential component of NMS by Pope et al.[3] and Adityanjee,[7] but NMS can be diagnosed without them.[2,4,6] The presence of mental status changes consistent with delirium has central importance in criteria proposed by Adityanjee[7] but is non-essential in most other criteria.[2–6] When considering a diagnosis of NMS in atypical presentations, an approach that permits the absence of one or more of the core components of NMS should be considered. It is important for clinicians to have a heightened understanding and be vigilant in monitoring for side effects from medications.[8,9]

Our patient presented with muscle rigidity and elevations in serum CK as well as alterations in mental status consistent with delirium. Although fever and autonomic signs were absent, the clinical and metabolic improvements following the discontinuation of the offending drugs suggest the diagnosis of atypical NMS, other conditions having been ruled out. It should be noted that our patient was prescribed benztropine in conjuction with ziprasidone. Given that the former is known to be effective in the initial treatment of NMS, his presentation may have been muted. There remains question about the unique contribution of ziprasidone and quetiapine in his NMS. A review of the literature of NMS with atypical antipsychotics showed published cases with ziprasidone, quetiapine, clozapine, olanzapine, risperidone, and aripiprazole.[8,10–12]

Conclusion

In summary, the standard approach to NMS includes recognizing the diagnosis early, excluding alternative causes of the symptoms, discontinuing suspected triggering drugs, and initiating treatment. This includes the use of dopaminergic agents such as bromocriptine, levodopa, or amantadine; and oxidative phosphorylation decouplers and muscle relaxants such as dantrolene and benzodiazepines. It is important to manage agitation or behavioural disturbances, which can be part of the underlying psychiatric disorder or a response to the NMS itself. Although atypical antipsychotics may be distinguished from typical antipsychotics by their ability to alleviate psychotic symptoms with minimal extrapyramidal side effects, all of these drugs have the potential to induce NMS. It is prudent for clinicians to be aware that polypharmacy with antipsychotics, medication changes or dose escalations, or even steady-state dosages are all risk factors for developing NMS.

References

1. Haddad PM. Neuroleptic malignant syndrome may be caused by other drugs. BMJ 1994;308(6922):200.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington (DC): American Psychiatric Association; 2000.
3. Pope JR, Keck PE, McElroy SL. Frequency and presentation of neuroleptic malignant presentation syndrome in a large psychiatric hospital. Am J Psychiatry 1986;143(10):1227–33.
4. Caroff SN, Mann SC, Lazarus A, et al. Neuroleptic malignant syndrome: diagnostic issues. Psychiatr Ann 1991;21:130–47.
5. Levenson JL. Neuroleptic malignant syndrome. Am J Psychiatry 1985;142(101):1137–45.
6. Addonizio G, Susman VL, Roth SD. Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. Am J Psychiatry 1986;143(12):1587–90.
7. Adityanjee. The spectrum concept and prevalence of neuroleptic malignant syndrome. Am J Psychiatry 1988;145(8):1041.
8. Troller JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. CNS Drugs 2009;23(6):477–92.
9. Ananth J, Parameswaran S, Gunatilake S, et al. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry 2004;65:464–70.
10. Farver DK. Neuroleptic malignant syndrome induced by atypical antipsychotics. Expert Opin Drug Safety 2003;2:21–35.
11. Ozen ME, Yumru M, Savas HA, et al. Neuroleptic malignant syndrome induced by ziprasidone on the second day of treatment. World J Biol Psychiatr 2007;8(1):42–4.
12. Leibold J, Patel V, Hasan RA. Neuroleptic malignant syndrome associated with ziprasidone in an adolescent. Clin Ther 2004;26:1105–8.

Failure to Cope?

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During my first week of rotation on the Acute Care Medicine Clinical Teaching Unit (CTU), I was introduced to the term "failure to cope," which in the 2 years leading up to clerkship I had never heard before. I soon learned that this term is used as a label, and catch-all classification, for patients who are deemed not to have any serious acute medical conditions but who are unable to cope with life at home and, as a default, are admitted to the hospital. My interactions with a particular patient who had the failure-to-cope label attached to her diagnosis serve to illustrate how the use of this term can be both inappropriate and, in my opinion, grossly inaccurate.

Mrs. H is a 90-year-old woman who came to the hospital from home because of worsening right hip pain. For close to 2 years, Mrs. H had suffered some level of pain in her right hip, but was finally prompted to come to hospital when the pain became so severe that she was unable to move. After being seen in the emergency room, Mrs. H was admitted to our medical team with the diagnosis failure to cope, and investigations began to try and establish a cause for the debilitating pain she was experiencing.

Hip pain was nothing new to Mrs. H as she had been experiencing hip discomfort since her family doctor diagnosed her with osteoarthritis of the hip 2 years previously. Mrs. H was not one to complain, however. When I asked her if she felt any frustration from having to deal with a chronically painful condition, she told me, "You just have to roll with the punches." This statement expressed to me a remarkably positive attitude, one that Mrs. H demonstrated throughout her stay in the hospital, and it also helped me to understand why I feel that she is the direct opposite of what is implied by the statement failure to cope.

Mrs. H has been living alone in her apartment since the death of her husband 14 years ago. Living alone was an adjustment for her at first; but she said she got used to it over time, and now she has no desire to leave or move into an assisted-living facility. Mrs. H is independent in almost every aspect of her life, and she is very proud of this. She has also established a strong network of friends, most of whom live in her apartment building and are in regular contact with her. Living on her own became more complicated earlier in the year after her brother, who had helped with the management of her finances among other things, suddenly passed away. When I asked her about how she was coping with this loss, Mrs. H said that it had been difficult, but that she was getting help, from her niece as well as from the employees at her bank, in the areas in which she used to receive assistance from her brother.

What is easy to forget when talking with Mrs. H is that for more than 6 years she has been legally blind. Mrs. H describes the loss of her sight as a setback, but just something that she realized she would have to adjust to – which is what she did. Adjustments took the form of leaving objects in specific places and learning how to properly use a cane to navigate her apartment. The hardest thing to get used was not being able to read, as she had been an avid reader prior to the loss of her sight.

The experience of being admitted to hospital provided some unique challenges to Mrs. H with regards to her visual impairment. Navigating an unfamiliar setting and not being at home where she knew where everything was, was somewhat difficult for her at first. Mrs. H said that as time progressed, she got used to her new setting; the only challenging part was when people would move an object that she had put down in a specific place, making it difficult to for her to find it again.

Early in Mrs. H's hospital course, the hip pain was very severe and the pain management regimen that we prescribed did not seem to be very effective in controlling her pain. Over time, the medication regimen was adjusted to better control her pain but still did not provide complete relief. When asked if the experience of having poorly managed pain was frustrating, Mrs. H said no, and that she felt that she had been receiving very good care.

Using magnetic resonance imaging, we determined that Mrs. H in fact had degenerative disc disease that was likely causing nerve impingement, thus providing a plausible explanation for the increased pain that she had been experiencing. By working enthusiastically with physiotherapy, and with improved pain

management, Mrs. H has been able to slowly regain her mobility. Throughout her course of physiotherapy, Mrs. H said she remained determined to regain her mobility so that she could return to living independently at home. When I spoke with Mrs. H before her transfer to the geriatric rehabilitation unit, she told me that she felt that she would be able to carry her enthusiastic and optimistic attitude forward into the next stage of her treatment.

The theme that emerged from my conversations with Mrs. H is best captured by her statement that "you just have to roll with the punches." Despite several setbacks in her lifetime – whether it was the sudden death of her husband, the loss of her vision, or living with chronic pain – Mrs. H remains a very optimistic person who has proven herself capable of adapting to new situations. When I asked her about the source of her positive attitude, Mrs. H was unsure, but said she felt it might have something to do with having lived through the Great Depression. Perhaps, she speculated, the uncertainty of that time and the fact that she worked odd jobs in order to help her family, instilled in her the importance of adaptability that she carried with her throughout the rest of her life. What is clear from my discussions with her is that the term "failure to cope" falls far short of describing Mrs. H's condition, as she has displayed considerable ability to adapt her life to the challenges that she has faced. The failure-to-cope label implies many things about our patients that we may not intend, and perhaps it would be for the best if its usage was stopped.

Outpatient Management of Hyperglycemia: What We Have Learned in the Past 90 Years, Since the Discovery of Insulin

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The year 2011 marks the 90th anniversary of the discovery of insulin. Banting, McLeod, Best, and Collip came together in the hot summer of 1921 in the Toronto Labs. Banting and McLeod won the Nobel Prize for this discovery. All four deserve recognition for this outstanding achievement. Diabetic patients have higher mortality at any age, whether it is from hypoglycemia in young person with type 1 diabetes or a heart attack in an older person with type 2. Visits to family doctors by patients with erectile dysfunction, neuropathy, retinopathy, foot ulcers, and psychosocial issues such as depression are on the increase. Hypertension, heart failure, stroke, renal disease, myocardial infarction, and lower limb amputation contribute to growing hospital costs. In the world today, 370 million people have diabetes: there is prodigious growth in third-world countries such as China and India, where lifestyles are changing rapidly. The United Nations has recognized diabetes as a major health issue in the world today (Figure 1).

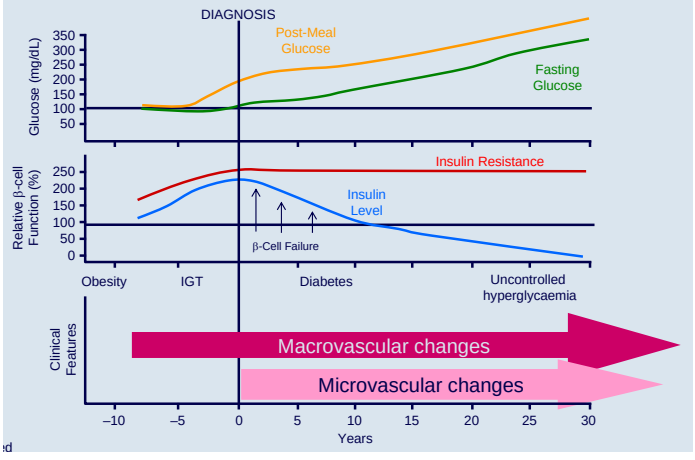


Figure 1. Natural progression of type 2 diabetes. IGT = impaired glucose tolerance.

Source: Adapted from Type 2 Diabetes Basics. Minneapolis (MN): International Diabetes Center; 2000.

Clinical Vignette

A 50-year-old female teacher controls her diabetes with diet and twice-daily metformin 500 mg. She checks her blood sugar each morning before breakfast, and records levels between 7 and 10 mmol/L. Her metformin dose is doubled, but her A1c climbs from 7.1 to 7.9%. Despite a diet low in sugar and fats, her weight seems static, and she blames a lifestyle that makes exercise difficult. Although she has no symptoms, she is concerned about the potential for diabetic complications.

She is overweight (height 168 cm [5 ft. 6 in.], weight 92 kg [203 lb.], body mass index [BMI] 33), and has a waist circumference of 94 cm (normal <88 cm). Her blood pressure averages 132/78 on angiotensin-converting enzyme (ACE) inhibitor therapy. She does not have neuropathy, and only mild retinopathy is evident. Her cardiovascular examination is unremarkable, and her peripheral pulses are good. Vibration sensation and reflexes are normal.

Her fasting blood glucose is 9.7 mmol/L, and her A1c 8.0%. Her urinary albumin-to-creatinine ratio (ACR), creatinine level, and liver profile are normal. Her low-density lipoprotein (LDL) cholesterol is 1.8 mmol/L, and her creatine kinase (CK) level is slightly elevated. What is the glycemic goal for this patient? Canadian guidelines for this patient suggest an A1c of <7.0%, but lower may be better if this can be achieved without hypoglycemic episodes. So what is our next step in her management (Figure 2)? Should we add

- sulphonylurea,
- a dipeptidyl peptidase 4 (DPP-4) inhibitor ,
- thiazolidinedione,
- a glucagon-like peptide 1 (GLP-1) agonist,
- meglitinide,
- insulin, or
- acarbose?

*This article was written by Dr. Hector Baillie, former editor-in-chief of *Canadian Journal of General Internal Medicine*, based on Dr. Zinman's presentation at the 2011 CSIM Annual Conference, in Halifax, Nova Scotia.

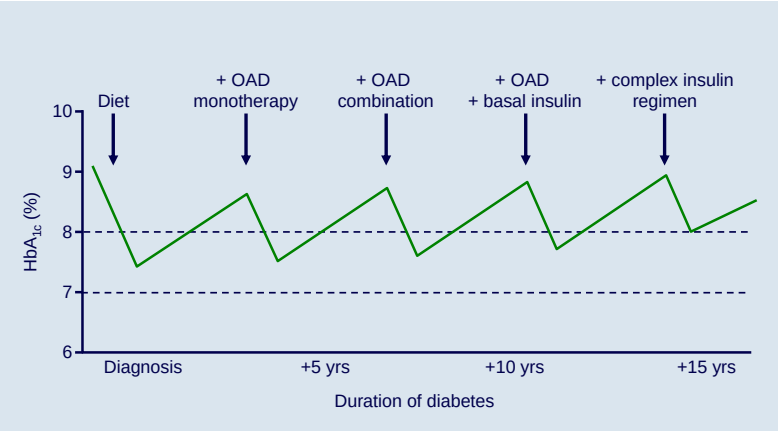


Figure 2. Traditional stepwise approach: treat to failure. OAD = oral antidiabetic.

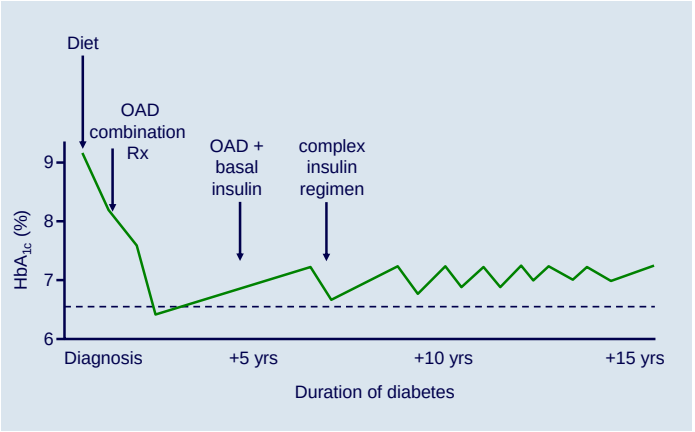
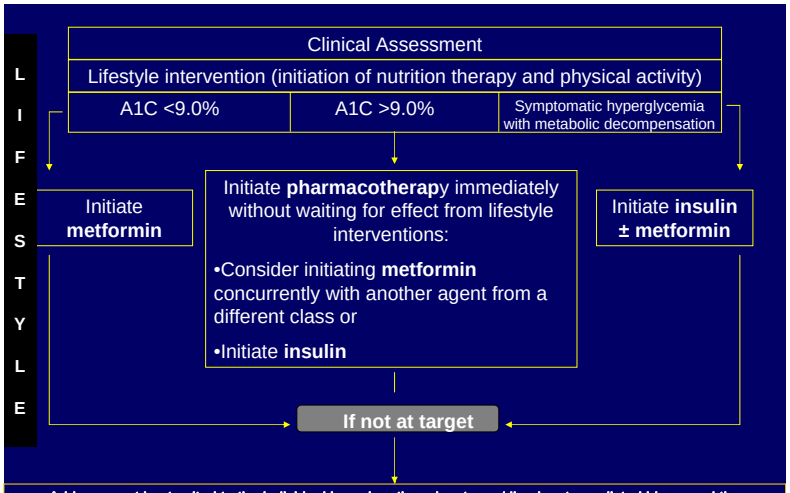


Figure 3. Proactive diabetes management: treat to target. OAD = oral antidiabetic.



Add an agent best suited to the individual based on the advantages/disadvantages listed bleow and the information contained in Table 1 *(agents listed in alphabetical order)*

Class	*A1C*	*Hypoglycemia*	*Other advantages*	*Other disadvantages*
Alpha-glucosidase inhibitor	↓	Rare	Improved postprandial control weight neutral	GI side effects
Incretin agent: DPP-4 inhibitor	↓ to ↓↓	Rare	Improved postprandial control weight neutral	New agent (unknown long-term safety)
Insulin	↓↓↓	Yes	No dose ceiling Many types, flexible regimes	Weight gain
Insulin secretagogue: **Meglitinide**	↓ to ↓↓	Yes*	Improved postprandial control	Requires TID to QID dosing
Sulfonylureas	↓↓	Yes	Newer sulfonylureas (gliclazide, glimepiride) are associated with less hypoglycemia than glyburide	Weight gain *less hypoglycemia in the context of missed meals
TZD	↓↓	Rare	Durable monotherapy	Requires 6-12 weeks for maximal effect Edema, rare CHF, rare fractures in females
Weight loss agent	↓	None	Weight loss	GI side effects (orlistat) Increased heart rate/BP (subutramine)

Figure 4. Management of hyperglycemia in type 2 diabetes. DPP = dipeptidyl peptidase; TZD = thiazolidinedione.

Are we setting patients up for failure? When diet fails, we add another oral agent, and then another, and then insulin. Patients on this schedule of ongoing failure become less motivated to comply with escalating regimes. Should we change our approach, recognizing that this complex disease with multiple pathophysiological pathways requires the introduction of combination therapy early on in the disease process (Figure 3)?

Shah et al. asked, "What do doctors do for patients with an A1c >8%?"[1] They found that 45% of specialists added new drugs, compared with 37% of family doctors. It seemed that specialists were more comfortable adding insulin. Therapeutic inertia continues to be a problem: often nothing is done for 24 months or more. The Canadian guidelines[2] suggest several approaches to timely interventions in this situation, but the list is purely alphabetical and lacks specific guidance (Figure 4).

A consensus algorithm developed for the American Diabetes Association was published in 2008.[3] This recommended A1c levels of <7%, the initiation of lifestyle changes and metformin at diagnosis, and the rapid addition of new medications and regimens (in particular, insulin therapy) when targets were not achieved.

Zinman has suggested a modification of this approach, encouraging the addition of basal insulin to lifestyle + metformin as step 2. The use of some sulphonylurea drugs, such as glyburide, is discouraged because of their lack of long-term durability and potential for harm (hypoglycemia). Alternatives to insulin were DPP-4

inhibitors and GLP-1 agonists. Pioglitazone could be considered at low doses, noting the potential for weight gain and possible bladder toxicity.

What are the desirable characteristics of a glucose-lowering agent, over and above morbidity and mortality outcomes: safety and tolerability; efficacy; a low risk of hypoglycemia; the absence of weight gain; a complementary mechanism of action with other therapies; durability; and, lastly, added value (e.g., improving beta cell function or improving the lipid profile).

Incretins have some of these characteristics. These are endocrine factors released by the gut in response to nutrient intake, especially carbohydrates, which augment insulin secretion and suppress glucagon release *in a glucose-dependent fashion*. The "incretin effect" has been known for years. An oral glucose load stimulates a greater release of insulin than an intravenous glucose bolus due to incretin-mediated glucose-dependent pathways. In diabetes, there seems to be a deficiency or blunting of this response. A classification of GLP-1 mimetics and analogues and DPP-4 inhibitors (which extend the GLP-1 half-life by inhibiting their degradation) are listed in Table 1.

The 3 AMIGOs trials[4–6] showed that the GLP-1 mimetic exenatide, added to metformin/sulphonylurea/both, led to reasonable glucose lowering (a fall in A1c of 0.8%; Figure 5) – and also weight loss (Figure 6).

GLP-1 agonists liraglutide and exenatide differ significantly in their amino acid sequencing. Liraglutide (NovoNordisk) has a much longer half-life and has been studied extensively, demonstrating reductions in A1c of 1.3–1.4% versus placebo. Liraglutide use has been associated with a 3–4 kg weight loss compared with insulin-based therapy, and 1.8–2.9 kg compared with other regimes. In fact, 25% of patients lose an impressive 7 kg in weight by mechanisms unrelated to the nausea sometimes seen shortly after medication initiation. Liraglutide also lowers blood pressure by 2–6 mm Hg and has a very low incidence of hypoglycemia compared with the sulphonylurea group of drugs (Figure 7).

Incretin therapies are being extensively studied for safety. These long-term controlled trials will document whether there are safety issues related to pancreatitis (DPP-4 and GLP-1), medullary thyroid carcinoma (GLP-1), cardiovascular outcomes (DPP-4 and GLP-1), Stevens-Johnson syndrome (DPP-4), and antibody formation (GLP-1).

In 1925, J. J. R. McLeod and W. R. Campbell stated, "In using insulin it would, of course, be ideal if it could be supplied so as to imitate the natural process." Compared with therapies such as thyroid supplementation, this is a huge challenge. Insulin levels rise with each meal to maintain narrow glucose excursion. Why should we use insulin early on in type 2 diabetes? Well, it is effective in lowering glucose levels, is easy to titrate, rests the beta cell, reduces free fatty acids and inflammatory markers, and helps endothelial function. Why haven't health care providers embraced early use of insulin? We tend to threaten patients with "the needle" if they haven't reached targets, and thus propagate the message of treatment

Table 1. Incretins: New Therapies in Diabetes

GLP-1 Mimetics
• Exenatide
• Exenatide LAR
GLP-1 Analogue
• Liraglutide
Incretin Enhancers (DPP-4 Inhibitors)
• Vildagliptin
• Saxagliptin
• Sitagliptin

DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; LAR = long-acting release.

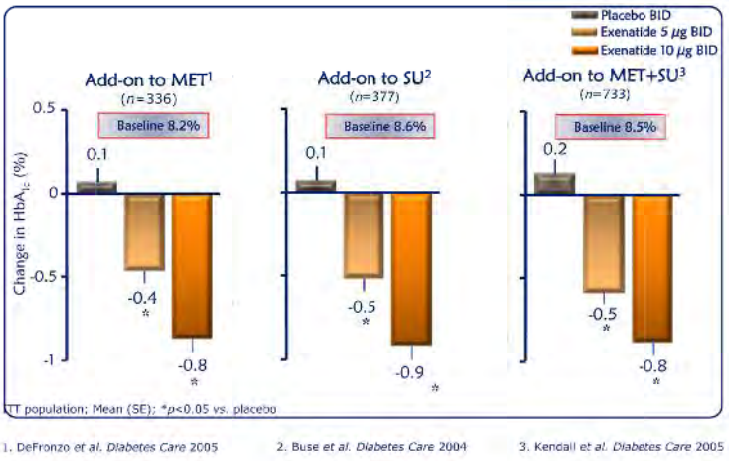


Figure 5. Exenatide: HbA1c changes after 30 weeks.

Sources: Data from the 3 AMIGOs trials.[4–6]

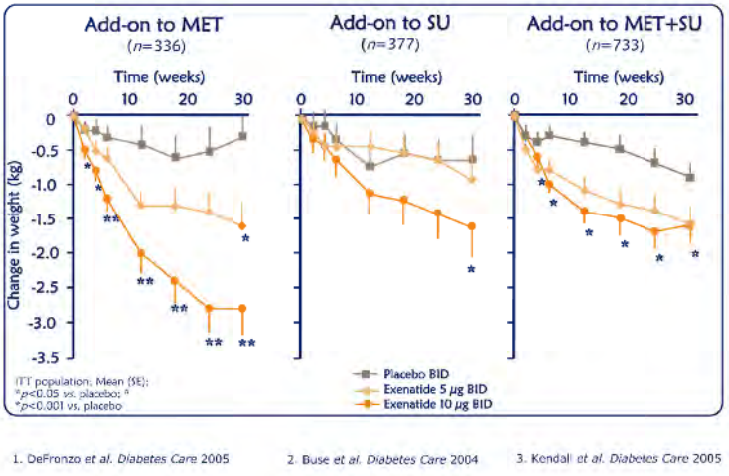


Figure 6. Exenatide: weight changes over 30 weeks.

Sources: Data from the 3 AMIGOs trials.[4–6]

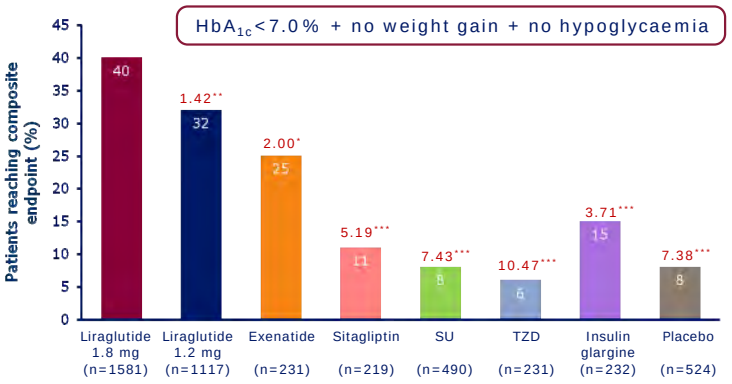


Figure 7. Liraglutide composite end points from phase 3 studies. SU = sulphonylurea; TZD = thiazolidinedione. Odds-ratio of achieving composite end point with liraglutide 1.8 mg is superior, with *$p < .01$; **$p < .001$, ***$p < .0001$."

Source: Data from Zinman et al.[7]

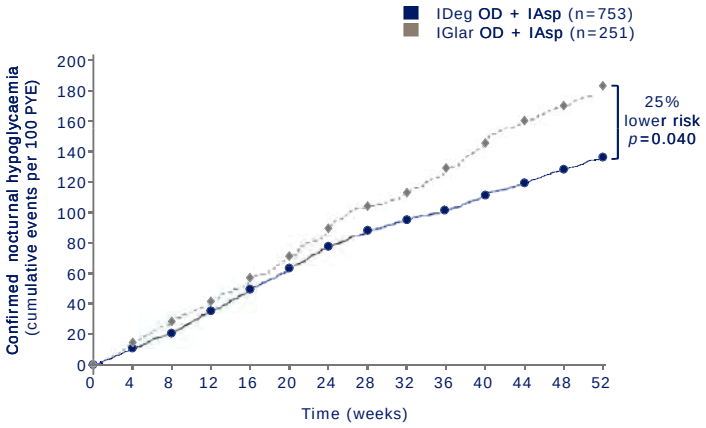


Figure 8. Confirmed nocturnal hypoglycemia for degludec versus glargine. PYE = patient-years of exposure. Comparisons: Estimates adjusted for multiple covariates."

Source: Data from Garber et al.[8]

failure. Patients may fear the pain of injections, hypoglycemia, and the weight gain associated with insulin. Is "insulin resistance" best thought of as the *resistance of providers* to prescribe the drug, and if so in sufficient amounts to reach targets?

Returning to our case, should we prescribe a (1) pre-mix insulin bid, (2) morning or nighttime basal analogue, (3) basal-bolus therapy, (4) nighttime NPH insulin, or (5) rapid-acting analogue insulin before the largest meal?

Basal Insulins

NPH, glargine, and detemir (0.4 U/kg) have been studied. The glucose response to NPH is quite variable compared with glargine and detemir.

Research is under way to make new long-acting insulins. For example, degludec's molecular structure is modified with fatty acid to form hexemers (dihexemers) in a vial. These dihexemers line up to form long extended chains in the subcutaneous space, which slowly disassemble as the zinc moiety breaks off. After a few days, the system is at steady state and provides an extremely stable depot of insulin therapy. Studies comparing degludec to glargine (in combination with rapid-acting insulin) give identical A1c results. As part of a basal-bolus insulin regimen, combined with metformin and pioglitazone, degludec had a significantly lower incidence of nocturnal hypoglycemia than glargine (Figure 8).[8]

Conclusion

Type 2 diabetes is a progressive disease, and most patients need rapid addition of new therapies. The addition of GLP-1 agonists or DPP-4 antagonists early on is now being evaluated in randomized controlled trials. Early initiation of basal insulin therapy should be considered in a more positive light.

References

1. Shah BR, Hux JE, Laupacis A, et al. Clinical inertia in response to inadequate glycemic control. Diabetes Care 2005;28:600–6.
2. Canadian Diabetes Association. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32 Suppl 1.
3. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care 2008;31:1–11.
4. DeFronzo et al. Diabetes Care 2005.
5. Buse et al. Diabetes Care 2004.
6. Kendall et al. Diabetes Care 2005.
7. Zinman B, Schmidt WE, Moses A, et al. Achieving a clinically relevant composite outcome of an HbA1c of <7% without weight gain or hypoglycemia in type 2 diabetes: a meta-analysis of the liraglutide trial programme. Diabetes Obes Metab 2012;14:77–82.
8. Garber et al. American Diabetes Association; 2011.

The European School of Internal Medicine Experience

Leena Amin MD

About the Author

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To try to catch a glimpse of another's world through his eyes can be quite an amazing thing. To now see your own world through new eyes, enlightening. And, perhaps most exquisite of all, is to come to learn that while your worlds may appear different at face value, a closer examination can reveal that a different scene can still give the same view. This is my attempt to reconcile, with words, my experience at the European School of Internal Medicine (ESIM) 2011.

I would first and foremost like to thank the Canadian Society of Internal Medicine for honouring me with the opportunity to attend this meeting in England this past autumn. The conference brought together senior postgraduate representatives with a strong interest in general internal medicine from over 26 different, far-reaching countries such as Iceland, Tunisia, and Israel. There were both formal and informal activities to facilitate our learning from one another about our different and common experiences, and approaches to internal medicine within our respective countries.

A full curriculum, plentiful with scientific lectureship on current topics within internal medicine, was delivered by professors from a variety of countries, including Denmark, England, Spain, and by our very own Dr. Linda Snell, who gave a fantastic workshop highlighting Canada as a leader in medical education. A number of students remarked at how formidable and rigorous they perceived our techniques of teaching, evaluation, and feedback in postgraduate curricula. Many trainees attested that they learned new skills that they would like to incorporate into their own residency programs.

Other great features of the conference were workshops involving clinical-pathology case conferences to discuss complex diagnoses and management – like Dr. House on a global scale. Participants also presented interesting cases from their respective countries, which, trainees agreed, were the highlight of the conference. Though we may have different approaches, we often arrived at the same answer, a curious and wonderful theme of this meeting. I certainly became even more appreciative of my unique training in Canada insofar as, with our diverse population, we have the opportunity to encounter and care for patients with an extensive spectrum of diseases that originate from virtually all over the world. Many European

The representatives from Canada singing our French national anthem for the international attendees to appreciate! *Left to right:* Dr. Karen Okraneic, Dr. Leena Amin, Dr. Linda Snell, and Ms. Bev Rowat.

trainees were impressed at the depth and vast scope of practice of the general internist in Canada.

Other workshops addressed issues that pertain to all postgraduate trainees, regardless of the country in which they practise. A particularly interesting discussion was around the role and future of general internal medicine. While in Canada the role of the general internist is often being redefined, it was surprising to learn that in many countries, the role itself lacks explicit existence. Some European countries encourage subspecialization so fervently that, in Denmark, for example, the entire specialty of internal medicine may become extinct. Many European delegates expressed a concern that a return to generalism within their countries is strongly needed to meet the growing needs of the aging population and increasing complexity of multi-system diseases. These discussions sounded like those here at home, and it was interesting to hear these same concerns (in various languages) across the pond as well.

National licensure also varied across countries in Europe whereby some countries, like Italy, require entrance examinations specifically into internal medicine, while other countries, like Holland, have no formal examination process at the end of residency. Other countries, Estonia, for example, train some subspecialists such as gastro-enterologists in a direct program from medical school, without formal training years in core internal medicine. Learning about our differences was both interesting and helpful to understand the issues facing residents from all over Europe. European-legislated maximum work hours per week were also a contentious issue. Needless to say, Canada is not the only country striving for the optimal balance between clinical training requirements and resident well-being.

Of course, the informal social program was amazing. Imagine meeting people from such different parts of the world and going out on the town, for laughs, questions, and great dining. At any given time, about seven different languages float across the table, with exchanges between people who, only days prior, were strangers but are now forming lasting friendships. I met people from countries I have not yet visited; and learning about how their health care context is directly impacted by the socio-political climate of their native countries not only opened my eyes but also forced me to examine our own health care system from a new perspective. For this, I am exceedingly grateful. I think the best way to do justice to the experience of ESIM 2011 would be to strongly encourage the initiation of a Canadian School of Internal Medicine in our very own backyard.

BRILINTA®
ticagrelor tablets

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Platelet Aggregation Inhibitor

INDICATIONS AND CLINICAL USE: BRILINTA (ticagrelor), co-administered with acetylsalicylic acid (ASA), is indicated for the secondary prevention of atherothrombotic events in patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non–ST Elevation Myocardial Infarction [NSTEMI] or ST Elevation Myocardial Infarction [STEMI]) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG).

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, BRILINTA is recommended to be co-administered with low maintenance dose ASA (75-150 mg daily).

Pediatrics (<18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

CONTRAINDICATIONS: BRILINTA (ticagrelor) is contraindicated in:

- Patients who are hypersensitive to this medication or to any ingredient in the formulation
- Patients who have active pathological bleeding such as peptic ulcer or intracranial hemorrhage
- Patients with a history of intracranial hemorrhage
- Patients with moderate to severe hepatic impairment
- Patients who are also taking strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir), as it may lead to a substantial increase in exposure to ticagrelor

SPECIAL POPULATIONS:

Pregnant Women: The safety of BRILINTA during pregnancy has not been established, as no clinical study has been conducted in pregnant women and limited clinical data on exposure to BRILINTA during pregnancy are available. Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy.

Nursing Women: It is not known whether this drug is excreted in human milk, as no clinical study has been conducted in lactating women. Studies in rats have shown that ticagrelor and its active metabolites are excreted in milk. Therefore, the use of BRILINTA during breastfeeding is not recommended.

Geriatrics (≥65 years of age): In PLATO, 43.1% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Pediatrics (<18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

Hepatic Impairment: Use of BRILINTA is contraindicated in patients with moderate or severe hepatic impairment.

Renal Impairment: No dose adjustment is necessary for patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy. Creatinine levels may increase during treatment with BRILINTA. The mechanism has not been identified. Renal function should be monitored in the course of patient management.

Uric Acid Increase: In PLATO, patients on BRILINTA had a higher risk of hyperuricemia than those receiving clopidogrel. Caution should be exercised when administering BRILINTA to patients with history of hyperuricemia or gouty arthritis. As a precautionary measure, the use of BRILINTA in patients with uric acid nephropathy is discouraged.

Safety Information

WARNINGS AND PRECAUTIONS:

General

Bleeding Risk: As with other antiplatelet agents, the use of BRILINTA (ticagrelor) in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events.

If clinically indicated, BRILINTA should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g., due to recent trauma, recent surgery, active or recent gastrointestinal bleeding, or moderate hepatic impairment). The use of BRILINTA is contraindicated in patients with active pathological bleeding, in those with history of intracranial hemorrhage, and moderate to severe hepatic impairment.
- Patients requiring oral anticoagulants (e.g., warfarin) and/or fibrinolytics agents (within 24 hours of BRILINTA dosing). Such agents confer an independent bleeding risk as they function in a distinct and complementary mechanism of hemostasis compared to BRILINTA. The combination of BRILINTA with either of these classes of drugs has not been studied.
  - **Warfarin Therapy:** Due to an increased propensity to bleed, caution is advised in patients taking warfarin during BRILINTA therapy. A specific drug-drug interaction study with warfarin has not been performed.
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding, e.g., non-steroidal anti-inflammatory drugs (NSAIDs).

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. Since co-administration of BRILINTA with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may augment hemostasis. BRILINTA may be resumed after the cause of bleeding has been identified and controlled.

Maintenance Dose Acetylsalicylic acid (ASA): Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, co-administration of BRILINTA and high maintenance dose ASA (>150 mg daily) is not recommended.

Cytochrome P450 3A4 Strong Inhibitors: Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor.

Peri-Operative Considerations

Surgery: If a patient requires surgery, clinicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.

To minimize the risk of bleeding, if a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery.

Respiratory

Dyspnea: In PLATO, approximately 13.8% of patients randomized to BRILINTA, versus 7.8% for clopidogrel, reported dyspnea, including dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea and nocturnal dyspnea. The dyspnea is usually mild to moderate in intensity and often resolves during continued BRILINTA treatment. The mechanism has not yet been elucidated. If a patient reports new, prolonged or worsened dyspnea this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE:

Adverse Drug Reaction Overview: The commonly reported adverse events in patients treated with BRILINTA (ticagrelor) were dyspnea, headache and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group (see Table 1).

Table 1: Summary of Adverse Events (Regardless of Causality) Reported for ≥1% of Patients in Either Group (PLATO)

Adverse Event (System Organ Class)	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
Blood and Lymphatic System Disorders		
Anemia	1.9	1.7
Cardiac Disorders		
Atrial fibrillation	4.2	4.6
Bradycardia[a]	2.9	2.9
Cardiac failure	2.3	2.6
Ventricular tachycardia	2.0	2.1
Palpitations	1.2	1.1
Angina pectoris	1.2	1.1
Sinus bradycardia	1.1	0.8
Ventricular extrasystoles	1.1	1.1
Ventricular fibrillation	0.8	1.0
Ear and Labyrinth Disorders		
Vertigo[b]	1.5	1.3
Gastrointestinal Disorders		
Nausea[b]	4.3	3.8
Diarrhea[b]	3.7	3.3
Vomiting[b]	2.5	2.3
Constipation[b]	2.2	2.6
Dyspepsia[b]	2.0	1.8
Abdominal pain upper	1.9	2.0
Abdominal pain[b]	1.5	1.2
General Disorders and Administration Site Conditions		
Non-cardiac chest pain	3.7	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5
Pyrexia	2.9	2.8
Edema peripheral	2.3	2.5
Asthenia	2.0	2.1
Hemorrhages or bleeding		
Epistaxis[b]	6.0	3.4
Contusion	3.9	2.0
Hematoma	2.2	1.3
Post-procedural hemorrhage[b]	2.1	2.0
Vessel puncture site hematoma	1.7	1.1
Ecchymosis	1.5	0.6
Infections and Infestations		
Urinary tract infection	2.0	1.8
Hematuria	1.9	1.6
Nasopharyngitis	1.8	1.6
Pneumonia	1.4	1.9
Bronchitis	1.3	1.4
Metabolism and Nutrition Disorders		
Diabetes mellitus	1.2	1.1
Dyslipidemia	1.0	1.0
Hypercholesterolemia	1.0	0.9
Hypokalemia	1.6	1.5
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.6	3.3
Pain in extremity	2.1	2.3
Musculoskeletal chest pain	1.5	1.4
Musculoskeletal pain	1.5	1.5
Arthralgia	1.5	1.4
Myalgia	1.4	1.6
Nervous System Disorders		
Headache[b]	6.5	5.8
Dizziness[b]	4.5	3.9
Syncope	1.1	0.8
Psychiatric Disorders		
Anxiety	2.2	1.9
Insomnia	1.7	2.0
Depression	1.1	1.1
Renal and Urinary Disorders		
Renal failure	1.0	0.7
Respiratory Disorders		
Dyspnea[a,b]	12.0	6.5
Cough	4.9	4.6
Dyspnea exertional	1.9	1.4
Skin and Subcutaneous Tissue Disorders		
Rash[b]	1.8	1.7
Pruritus[b]	1.0	1.0
Vascular Disorders		
Hypertension	3.8	4.0
Hypotension	3.2	3.3

a Several MedDRA PT combined.
b These events have also been reported as Adverse Drug Reactions (possibly or probably related to BRILINTA).

DRUG INTERACTIONS: Cytochrome P450 (CYP) 3A4/5 are the major enzymes responsible for the metabolism of BRILINTA (ticagrelor) and the formation of the active metabolite. Clinical pharmacology and *in vitro* data show that there is a complex interaction between ticagrelor and CYP3A4/5. Indeed, depending on the substrate, ticagrelor and its active metabolite are shown to weakly inhibit or weakly activate CYP3A4/5 (see DETAILED PHARMACOLOGY). Therefore, co-administration of BRILINTA and CYP3A4/5 substrates with narrow therapeutic indices is not recommended. CYP enzymes 1A2, 2C19 and 2E1 do not contribute meaningfully *in vitro* to ticagrelor metabolism. BRILINTA is also a p-glycoprotein (P-gp) substrate and a weak inhibitor of P-gp.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
Fax toll-free to 1-866-678-6789, or
Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage-paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.

Administration

Recommended Dose and Dosage Adjustment

BRILINTA therapy should be initiated with a single 180 mg oral loading dose (two 90 mg tablets) and then continued at 90 mg twice daily. Patients taking BRILINTA should also take acetylsalicylic acid (ASA) daily, unless specifically contraindicated. Following an initial loading dose of ASA, BRILINTA should be used with a daily maintenance dose of ASA of 75-150 mg.

BRILINTA can be taken orally with or without food. In a study of healthy subjects, ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These changes are considered of minimal clinical significance. BRILINTA was administered without regard to food in PLATO.

Grapefruit juice interaction: A drug-drug interaction study with grapefruit juice has not been performed. Based on the pharmacokinetic data for ticagrelor, grapefruit juice is expected to increase ticagrelor exposure to a clinically insignificant extent. Therefore, BRILINTA can be taken with grapefruit juice.

Missed Dose

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

SUPPLEMENTAL PRODUCT INFORMATION

WARNINGS AND PRECAUTIONS:

Discontinuations: Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event, it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution.

Cardiovascular

Patients at Risk for Bradycardic Events: Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, the Phase III study (PLATO) excluded patients with an increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope and not protected with a pacemaker). Therefore, due to the limited clinical experience, BRILINTA should be used with caution in these patients.

In addition, caution should be exercised when administering BRILINTA concomitantly with drugs known to induce bradycardia. However, no evidence of clinically significant adverse interactions was observed in the PLATO trial during concomitant administration with one or more drugs known to induce bradycardia: in PLATO, 96% of patients took beta-blockers, 33% took diltiazem or verapamil (calcium channel blockers) and 4% took digoxin.

Neurologic

Effects on Ability to Drive and Use Machines: No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. BRILINTA has no or negligible influence on the ability to drive and use machines. During treatment for Acute Coronary Syndromes, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

Peri-Operative Considerations

In PLATO patients undergoing CABG, BRILINTA had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where BRILINTA had a higher rate of major bleeding.

Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel.

In the OFFSET study, mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, e.g., in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.

Adverse Drug Reaction Overview

In PLATO, a total of 6762 patients with Acute Coronary Syndromes (UA, NSTEMI and STEMI) were exposed to BRILINTA (180 mg loading dose followed by a 90 mg twice daily maintenance dose) for at least 6 months and up to 12 months for 3138 of them.

Serious adverse events were reported in a similar frequency between BRILINTA (20.2%) and clopidogrel (20.3%) treated patients. The most frequent serious adverse events observed were cardiac failure (1.1% vs. 1.0%), non-cardiac chest pain (0.9% vs. 0.9%) and dyspnea (0.7% vs. 0.4%).

The rate of study drug discontinuation because of adverse events was 7.4% for BRILINTA and 5.4% for clopidogrel. Dyspnea was the most common adverse event leading to study drug discontinuation for BRILINTA (0.9% for BRILINTA and 0.1% for clopidogrel).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Bleeding Events: The primary safety endpoint in the PLATO study was the composite endpoint of 'Total Major' bleeding, which consisted of the components of 'Major Fatal/Life-threatening' and 'Major Other'. Table 2 shows the 12-month rates of patients experiencing bleeding events in the PLATO study (PLATO-defined).

Table 2: Analysis of Overall Bleeding Events – PLATO-defined

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	*p*-value*
Primary Safety Endpoint			
Total Major	11.6	11.2	0.4336
Secondary Safety Endpoints			
Major Fatal/Life-threatening	5.8	5.8	0.6988
Combined Total Major + Minor	16.1	14.6	0.0084
Non-procedural Major	3.1	2.3	0.0058
Non-procedural Major + Minor	5.9	4.3	<0.0001
Non-CABG Total Major	4.5	3.8	0.0264
Non-CABG Major Fatal/Life-threatening	2.1	1.9	0.2516

*Nominal *p*-value not corrected for multiple testing.
Major Fatal/Life-threatening: Clinically apparent with >50 g/L decrease in hemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/L decrease in hemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor: Requires medical intervention to stop or treat bleeding.

There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel.

Location of 'Total Major + Minor' Bleeding (BRILINTA vs. clopidogrel): Intracranial 0.3% vs. 0.2%, pericardial 0.1% vs. 0.1%, retroperitoneal 0.03% vs. 0.03%, intraocular 0.02% vs. 0.04% and intra-articular 0.02% vs. 0.01%. Other common locations were in rank order of event frequency: gastrointestinal 1.8% vs. 1.5%, epistaxis 1.3% vs. 0.7%, urinary 0.5% vs. 0.4%, subcutaneous/dermal 0.5% vs. 0.4% and hemoptysis 0.1% vs. 0.08%.

Non-procedural Fatal Bleeding: There was no difference with BRILINTA compared to clopidogrel for overall non-procedural fatal bleeding. There were numerically more 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA (n=27 events, 0.3%) than with clopidogrel (n=14 events, 0.2%). Of the intracranial non-procedural bleeding events, 11 bleeding events with BRILINTA and 1 with clopidogrel were fatal. 'Major Fatal/Life-threatening' gastrointestinal bleeding was the same with BRILINTA and clopidogrel, with numerically more fatal events for clopidogrel (5) than for BRILINTA (none).

Bleeding in Subgroups Patient Population: Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Table 3 shows the overall rates of TIMI-defined bleeding events.

Table 3: Analysis of Overall Bleeding Events – TIMI-defined

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	*p*-value
Major	7.9	7.7	0.5669
Major + Minor	11.4	10.9	0.3272
Non-CABG Major	2.8	2.2	0.0246
Non-CABG Major + Minor	4.5	3.6	0.0093

TIMI Major: Clinically apparent with >50 g/L decrease in hemoglobin or intracranial hemorrhage.
TIMI Minor: Clinically apparent with 30 to ≤50 g/L decrease in hemoglobin.

Additional clinical Adverse Drug Reactions that were reported as possibly or probably related to BRILINTA are listed below by body system:

Common (≥1% to <10%)
- *Skin and subcutaneous tissue disorders:* subcutaneous or dermal bleeding
- *Gastrointestinal disorders:* gastrointestinal hemorrhages
- *Renal and urinary disorders:* urinary tract bleeding

Uncommon (≥0.1% to <1%)
- *Nervous system disorders:* intracranial hemorrhage (may be fatal or life threatening), confusion, paraesthesia
- *Gastrointestinal disorders:* gastritis, retroperitoneal hemorrhage
- *Eye disorders:* eye hemorrhage (intraocular, conjunctival, retinal)
- *Respiratory, thoracic and mediastinal disorders:* hemoptysis

Rare (≥0.01% to <0.1%)
- *Musculoskeletal connective tissue and bone:* hemarthrosis

DRUG INTERACTIONS:

Drug-Drug Interactions

Effects of Other Drugs on BRILINTA

Ketoconazole (Strong CYP3A4 Inhibitors): Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of ticagrelor's active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir and atazanavir) would be expected to have similar effects and are contraindicated with BRILINTA.

Diltiazem (Moderate CYP3A4 Inhibitors): Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% and AUC by 174% and decreased its active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole and verapamil) would be expected to have similar effects. These exposure changes are not considered clinically significant, and therefore can as well be co-administered with BRILINTA.

Rifampin and Other CYP3A4 Inducers: Co-administration of rifampin with ticagrelor decreased the ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of its active metabolite was unchanged and the AUC was decreased by 46%. Other CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA.

Others: Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and acetylsalicylic acid (ASA) did not have any effect on ticagrelor or its active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

Effects of BRILINTA on Other Drugs

Simvastatin: Co-administration of ticagrelor with simvastatin increased the simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on ticagrelor plasma levels. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin: Co-administration of atorvastatin and ticagrelor increased the atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Tolbutamide: Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which demonstrates ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the metabolism of other drugs metabolized via CYP2C9.

Warfarin: A drug-drug interaction study with warfarin has not been performed. As with other oral antiplatelet therapy, there is a potential for increased risk of bleeding, therefore, warfarin and BRILINTA should be co-administered with caution.

Oral Contraceptives: Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

Digoxin (P-gp Substrate): Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with BRILINTA.

Other Concomitant Therapy: In clinical studies, BRILINTA was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

DOSAGE AND ADMINISTRATION:

General

The PLATO trial data suggest the efficacy of BRILINTA (ticagrelor) relative to clopidogrel is associated with ASA dose during maintenance therapy. Patients receiving a low maintenance dose of ASA benefit more than those receiving a high maintenance dose of ASA. Because the data from patients receiving high maintenance dose ASA (>300 mg daily) do not provide conclusive evidence of the efficacy of BRILINTA compared to clopidogrel, high maintenance dose ASA (>150 mg daily) is not recommended for maintenance dual antiplatelet therapy with BRILINTA. There is no conclusive evidence regarding the underlying biological mechanism. Based on analysis of the available clinical data, it is recommended that BRILINTA be used with a daily low maintenance dose of ASA (75-150 mg).

Furthermore, no safety and efficacy data is available on the use of BRILINTA beyond one year treatment duration.

Recommended Dose and Dosage Adjustment

Switching from clopidogrel to BRILINTA: Patients can be switched from clopidogrel to BRILINTA without interruption of antiplatelet effect. This results in an absolute inhibition of platelet aggregation (IPA) increase of 26.4%. Conversely, switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5%. Clinicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel.

Dosing Considerations in Special Populations

Geriatrics (≥65 years of age): No dosage adjustment is required in elderly (≥65 years) patients.

Patients with Renal Insufficiency: No dosage adjustment is required in patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy.

Patients with Hepatic Insufficiency: No dosage adjustment is required in patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

OVERDOSAGE:

For management of suspected drug overdose, contact your regional Poison Control Centre.

Treatment

There is currently no known antidote to reverse the effects of BRILINTA (ticagrelor), and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs, appropriate supportive measures should be taken.

ACTION AND CLINICAL PHARMACOLOGY:

Pharmacodynamics

Inhibition of platelet aggregation (IPA) mediated by ticagrelor increases with increasing plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX), until almost complete inhibition is attained. The inhibition of platelet aggregation gradually decreases with declining plasma ticagrelor and active metabolite concentrations, as the IPA mediated by ticagrelor is reversible. Since ticagrelor reversibly binds to the $P2Y_{12}$ receptor, the recovery of platelet function is expected to be dependent on the plasma concentrations of ticagrelor and the active metabolite and not on the replacement of irreversibly inhibited platelets as with thienopyridine antiplatelet agents.

The IPA of ticagrelor is generally independent of factors such as race, hepatic or renal disease or co-administered ASA, heparin and enoxaparin.

Pharmacokinetics

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and its active metabolite are approximately dose proportional.

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The Prescribing Summary provides the most current information at the time of printing. For access to the most up-to-date information, view the full Product Monograph (prepared for health professionals) by visiting www.astrazeneca.ca or by contacting AstraZeneca Canada Inc.

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