PharmaNote

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New Evidence About an Old Drug: Role of Digoxin in Atrial Fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice and affects between 2.7-6.1 million Americans.[1] AF is characterized by rapid and disorganized atrial activation, which results in a loss of synchronized atrial contraction.[2] Without synchronization, the atria fail to eject blood properly, which reduces ventricular filling and stroke volume.[2] The chronic pharmacologic management of AF involves assessing the need for rate and/or rhythm control. A rate control strategy achieves an adequate heart rate to supply necessary cardiac output.[3] The choice of rate control depends on clinical symptoms, comorbidities and presence of heart failure (HF) with preserved or reduced left ventricular ejection fraction.[4] Three classes of medications are primarily used to reduce the ventricular rate during AF: beta-blockers, non-dihydropyridine calcium-channel blockers and digoxin.[4] The choice of whether to use rate control medications alone or in combination depends on clinical symptoms, hemodynamic status, comorbidities such as HF and potential side effects.[4] This article will focus on the use of digoxin in the chronic management of AF.

Digoxin is extracted from the leaves of *Digitalis lanata*. Digoxin has been in clinical use for more than 200 years with the first published report on the use digitalis dating back to 1785.[5] In the 1920's, the positive inotropic effects on the heart were elucidated.[6] Since the 1960's digoxin has been used clinically for rate control in patients with AF although its use has declined due to newer agents with improved tolerability, efficacy, safety and less side effects.[5] Despite the decline in use, digoxin is still utilized in about 30% of patients with AF worldwide.[7,8] Digoxin inhibits the sodium-potassium adenosine triphosphatase (ATPase) pump.[5] ATPase is an enzyme that regulates the quantity of sodium and potassium inside cells.[5] Through inhibition of this enzyme, intracellular concentrations of sodium are increased, which increases intracellular calcium.[5] Digoxin exerts its effects directly on cardiac muscle and indirectly on the autonomic nervous system.[9] The autonomic effects include vagomimetic action and baroreceptor sensitization, which increase the force and velocity of myocardial systolic contraction.[9] This decreases sympathetic nervous system activation, and slows the heart rate through decreased conduction velocity through the atrioventricular (AV) node.

Place in Therapy for Rate Control

Digoxin is typically not a first line rate control therapy in patients with AF. Current guidelines recommend digoxin for rate control in patients with AF with and without HF.[10,11] However, its use is limited by the potential for electrolyte imbalances, drug-drug interactions, delayed onset of action and a narrow therapeutic index.[5] Given these limitations, serum digoxin concentration (SDC) may be measured although there are no specific recommendations about SDC monitoring in the AF guidelines and SDC monitoring is not routinely done in the ambulatory care setting.

Preferred agents for rate control include beta-blockers and non-dihydropyridine calcium channel blockers due to their rapid onset and improved safety profile.[5] However, digoxin may be combined with beta-blockers or non-dihydropyridine calcium channel blockers to improve ventricular rate control during exercise.[10,11] Combination therapy may also be beneficial when physiological parameters limit up-titration of other rate control agents.[10,11] Since digoxin has no effects on blood pressure, it may also be used in patients with hypotension, as beta-blockers and non-dihydropyridine calcium channel blockers have greater effects on blood pressure.

Digoxin may also be considered in those with concomitant HF with a reduced ejection fraction and AF.[12] Physiologically, AF exacerbates HF due to a loss of atrial contribution to left ventricular filling, loss of biventricular pacing and or reduced filling time in the setting of a fast ventricular rate.[12,13] Although a mortality benefit has not been demonstrated in this patient population, digoxin has been shown to improve symptoms after optimizing traditional therapeutic options and does decrease hospitalizations due to HF.[14]

Digoxin should be avoided in patients with pre-excitation and AF, as it may increase ventricular response and result in ventricular fibrillation.[10] Digoxin should also be avoided in patients with Wolff-Parkinson-White syndrome, Lown-Ganong-Levine or atrioventricular reentrant tachycardia with an accessory pathway.[10]

Digoxin and Mortality

Data from several trials, post-hoc analyses and observational

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Table 1 | Evidence-Based Summary of Association Between Mortality and Digoxin Use

Trial	Study Design	Population	Findings
Association with mortality			
Chao et al[15]	Retrospective cohort	4,781 Taiwanese patients with AF	Increased all-cause mortality and ischemic stroke with digoxin
Freeman et al[16]	Retrospective cohort	14,787 American patients with AF and no prior HF or digoxin use	Increased all-cause mortality and all cause hospitalization with digoxin
Hallberg et al[17]	Prospective cohort	21,459 Swedish patients with AF and no HF	Increased mortality associated with digoxin use
Ouyang et al[18]	Meta-analysis	318,191 patients with AF	Increased all-cause mortality with digoxin use
Pastori et al[19]	Prospective cohort	815 patients with AF treated with VKAs	Increased all-cause and cardiovascular mortality with digoxin use
Qureshi et al[20]	Systematic review and meta-analysis	111,978 digoxin users and 389,643 non-digoxin users with AF	Increased all-cause mortality with digoxin use
Shah et al[21]	Retrospective cohort	100,599 patients with AF ± HF	Increased all-cause mortality with digoxin use (AF ± HF)
Turakhia et al[22]	Retrospective cohort	122,465 American VA patients with AF	Inconsistent increased all-cause mortality with digoxin
Vamos et al[23]	Meta-analysis	326,426 patients with AF	Increased all-cause mortality with digoxin use
Wang et al[24]	Meta-analysis	302,738 patients with AF	Increased all-cause mortality with digoxin use
Washam et al[25]	Post-hoc retrospective analysis of ROCKET-AF	14,171 patients with AF and moderate-to-high risk of stroke ± HF	Increased all-cause mortality, vascular death and sudden death in patients with AF
Whitbeck et al[26]	Post-hoc subgroup analysis of AFFIRM	1,377 patients with AF who received digoxin at baseline and continued throughout the study	Increased all-cause and cardiovascular mortality with digoxin use
Zeng et al[27]	Meta-analysis	586,594 patients with AF taking digoxin	Increased all-cause mortality, cardiovascular death, arrhythmic death, stroke in patients taking digoxin independent of age, sex, HF or beta-blocker usage
No association with mortality			
Chamaria et al[28]	Meta-analysis	321,944 patients with AF ± HF	No association to all-cause mortality when used for rate control
Friberg et al[29]	Prospective cohort	2,824 Swedish patients with AF	No association to mortality, MI, stroke, or HF-related hospitalizations with digoxin
Gheorghiade et al[30]	Post-hoc subgroup analysis of AFFIRM	878 patients with AF who received digoxin at baseline regardless of duration of therapy	No association to mortality or all-cause hospitalization with digoxin use
Rodriguez-Manero et al[31]	Prospective cohort	777 Spanish patients with AF	No association to all-cause mortality, admission for any cause, or admission for cardiovascular cause with digoxin use

AF = atrial fibrillation; **HF** = heart failure

studies have produced conflicting results about the effect of digoxin on cardiovascular outcomes in patients with AF. A summary of this evidence is shown in **Table 1**. Several studies have shown that digoxin is associated with mortality in patients with AF[15-27], although a smaller number of studies suggest that there is no association between mortality and digoxin use.[28-31] A critical limitation to the current data is the lack of randomization and it is unlikely that we will see future randomized controlled trials to evaluate mortality risk with digoxin. Interpretation of the current evidence is further complicated by different baseline patient characteristics, comorbidities, medications and different study designs.

Since digoxin is not a first-line pharmacologic agent for patients with AF, the patients included in studies may have had more comorbidities so a key consideration is whether the safety issues are related to the digoxin or the type of patients treated with digoxin. Since a majority of the evidence linking digoxin to increased mortality is observational in nature, it is difficult to establish digoxin use as a causative factor in increasing mortality in AF patients.

Does Serum Digoxin Concentration Matter?

The DIG (Digitalis Investigation Group) trial is the only randomized double blind prospective trial to date that enrolled HF patients in sinus rhythm and randomized them to receive digoxin or placebo with background ACE-I and diuretic therapy.[14] Digoxin did not reduce overall mortality but did reduce the rate of hospitalizations both overall and for worsening HF.[14] In the DIG-SDC trial, which was a post-hoc analysis of the DIG trial, higher SDC was associated with increased crude all-cause mortality (0.5-0.8 ng/mL, 29.9%; 0.9-1.1 ng/mL, 38.8%; and ≥1.2 ng/mL, 48%; P=0.006).[32] However the post-hoc analysis only included men since a small number of women had SDC measured in the DIG trial.[32] The take home with the DIG-SDC trial was that the effectiveness of digoxin therapy in men with HF and a left ventricular ejection fraction ≤45% might be optimized on digoxin in the SDC range of 0.5-0.8 ng/mL.[32] Since the DIG trial only included patients in sinus rhythm, the association between mortality and SDC in AF patients had previously remained unanswered.

The ARISTOTLE trial compared apixaban with warfarin on bleeding and embolic endpoints in patients with AF.[8] Approximately 40% of patients in ARISTOTLE had HF and more than 30% were on digoxin.[8] In a post-hoc analysis of ARISTOTLE data 17,897 of the 18,201 patients enrolled in the trial had data available on HF status and digoxin use.[33] The aim of this analysis was to explore the association between digoxin use and mortality according to SDC in patients with and without HF. Physicians within the ARISTOTLE study protocol were able to initiate antiarrhythmics and digoxin, which allowed for comparison of existing digoxin users and new digoxin users on mortality rates. The analysis also along included measurement of SDC at baseline.

Each patient who started taking digoxin during the study was matched with three controls that were not taking digoxin. An increased risk of death was observed with increasing SDC. For every 0.5 ng/mL increase in baseline SDC, the risk of death was increased 19%.[33] In patients whose digoxin level was ≥1.2 ng/mL, the death rate increased by 56% (P=0.001).[33] Patients who began taking digoxin during the study had a 78% increase in all cause mortality, and a 4-fold increase in the risk of sudden death (P<0.001).[33] This increase in mortality occurred despite adjusting for patients renal function, as digoxin is eliminated renally. While these results are concerning, it should be noted that this data is from a post-hoc analysis of ARISTOTLE data. Post-hoc analysis results may have the potential for unmeasured confounding factors and patients within the ARISTOTLE trial were not randomized to test the primary outcome of all-cause mortality with digoxin in patients with AF and HF.

Conclusion

In the absence of randomized controlled trial data demonstrating that digoxin is safe and efficacious, digoxin should be reserved as an alternative rate control agent in AF, particularly if symptoms can be alleviated with other rate control agents. Clinicians should consider using either beta-blockers or non-dihydropyridine calcium-channel blockers and refrain from using digoxin as monotherapy for rate control in AF. SDC monitoring is rarely done in the ambulatory care setting and monitoring is usually only warranted in patients with renal impairment, those with potential drug-drug interactions or if there is suspicion for digoxin toxicity. However, based on recent evidence from a post-hoc analysis of ARISTOTLE, SDC monitoring in patients with AF may be important to target SDC <1.2 ng/mL.

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Once Versus Twice-Daily Dosing of Insulin Glargine: A Comprehensive Review of the Literature

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Diabetes affects 29.1 million people in the United States which is about 9.3% of the population.[1] Approximately 21 million people have been diagnosed with diabetes; while roughly 8.1 million people are unaware that they have diabetes.[1] Patients with type 2 diabetes make up the majority of this population, while about 1.25 million patients have type 1 diabetes.[1] Characteristics of diabetes include decreased insulin secretion, decreased insulin sensitivity, or both. The overall goal for patients with diabetes is to reduce long-term complications, such as microvascular and macrovascular disease. The American Diabetes Association (ADA) and the American Associations of Clinical Endocrinologists (AACE) recommend initial drug therapy with metformin in patients with type 2 diabetes. Basal insulin may be add-on following initiation of metformin in select patient populations.[2,3] The AACE guidelines state that basal insulin may initially be started in combination with metformin in symptomatic patients with an HbA_{1c} greater than 9%. Conversely, the mainstay therapy for individuals with type 1 diabetes is exogenous insulin administration, due to the destruction of pancreatic beta cells that are responsible for the release of insulin.

Some patients may require twice daily dosing of insulin glargine in the event that once daily dosing does not provide full daily coverage due to inadequate absorption. Twice daily dosing has also been proposed to decrease rates of hypoglycemic events. The purpose of this article is to review the current literature surrounding, twice daily dosing of insulin glargine, discuss situations when twice daily dosing is favored over once daily dosing, and provide recommendations regarding initiating twice daily dosing of insulin glargine.

Pharmacology

Insulin promotes the storage of glucose, fat, and amino acids as well as preventing their breakdown. Insulin facilitates glucose uptake by muscle and adipose tissue leading to lower glucose concentrations, and inhibits glycogenolysis and gluconeogenesis. Additionally, insulin enhances lipogenesis and protein synthesis, while also inhibiting lipolysis and proteolysis. Insulin is metabolized by the liver and kidneys. In patients with hepatic impairment, some studies have shown increased circulating levels of insulin. Additionally, those with renal impairment may have increased response to a given dose of insulin. Insulin glargine has an onset of action of approximately 1.5 hours, and provides a consistent peak-less effect on glucose reduction over a median duration of 24 hours.[4]

Adverse Effects

Insulin glargine is generally well tolerated when monitored appropriately, however it is considered a high-risk medication. Firstly, injection site pain including pruritus and rash is common in patients. Most importantly, hypoglycemia may result from use

of any insulin, and thus patients should self-monitor blood glucose at home. Additionally, nocturnal hypoglycemia is common and should be monitored in patients at high-risk. Patients that are at high-risk include the elderly and those on intensive therapy. Certain drugs can also increase risk for hypoglycemic events, these include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), nonselective beta 2 blockers, and alcohol.[5] Patients should also be instructed to rotate injection sites to prevent lipodystrophy, and interestingly, patients who use insulin glargine have an increased incidence of infectious diseases.

Review of the Literature

Long-acting insulin glargine is traditionally dosed every 24 hours, however above a certain number of units (none is currently established) some providers may divide the dose and increase the dosing frequency to every 12 hours. The general rationale behind this transition to twice-daily dosing of insulin glargine is the thought that the body may not be able to absorb the insulin dose adequately if a large dose is administered. The 12-hour dosing regimen is also sometimes used in patients believed to be at greater risk for hypoglycemia. **Table 1** provides a summary of the current literature available, evaluating the glycemic impact of twice daily dosing with insulin glargine.

In 2002, Heise et al. studied whether there was evidence for accumulation of insulin glargine in patients with type 1 diabetes.[6] This study included 15 patients whose mean age was 36 ± 9 years and had a mean body mass index of 24.6 ± 2.2 kg/m^2. Patients were all previously on twice daily NPH or a continuous insulin infusion and pre-prandial regular insulin. These patients were on a maximum total insulin dose of 1 IU/kg/day. Exclusion criteria consisted of those with a history of unawareness of hypoglycemia events, history of seizure of coma in the past year due to a hypoglycemic event, treatment with a beta blocker or systemic steroids, and renal or hepatic impairment. Patients initially underwent a dose-finding phase to determine their optimal insulin glargine dose. Patients in this study received both basal insulin glargine and pre-prandial insulin lispro. Average basal insulin glargine requirements were 24 ± 6 units which patients injected into their abdominal tissue subcutaneously every night for 12 days. Free serum insulin concentrations were assessed on days 1, 4, and 11 to determine whether the dose of insulin glargine accumulated with time. To prevent possible interference from pre-prandial insulin lispro, patients fasted for 24 hours after their injections on days 1, 4, and 11. Free serum insulin concentrations were measured 5 minutes before insulin glargine injection on these days, and then at 24 hours after these injections. The mean free serum insulin levels were 79 pmol/l on day 1, 77 pmol/l on day 4, and 86 pmol/l on day 11. The elevated level on day 11 was due to 2 patients injecting insulin lispro prior to the measurement of their free serum insulin level. Overall, no significant difference was observed between the free serum insulin levels, indicating that insulin glargine did not appear to accumulate in patients with type 1 diabetes. However, a limitation of this study is the fact that the average dose of insulin glargine was 24 units; a relatively small amount compared to other patients who may require 100 units of insulin glargine or more daily.

In 2003, Hamann et al. conducted an open-label, randomized, parallel group, multicenter study investigating once daily dosing of insulin glargine administered before breakfast, before dinner, or at bedtime.[7] This studied was performed in order to determine if timing of insulin glargine had an effect on overall blood glucose control and episodes of hypoglycemia. This study was performed in 378 patients with type 1 diabetes who had been on basal-bolus therapy for at least the past 6 months. Patients were aged 40.9 ± 11.9 years, had HbA1c 5.5-9.8%, and diabetes duration 17.3 ± 11.5 years. Patients were initially screened for 1 to 4 weeks on their usual insulin regimen in order to determine their optimal total daily insulin dose before randomization. Patients previously on insulin glargine continued at the same unit dose after randomization, but those on other basal insulins that were administered more than once a day (>80% of patients) were switched to insulin glargine at 80% of their normal total daily insulin dose. Afterwards, patients were titrated up to optimal doses during the 24 week study period. Total daily insulin dose was similar between all 3 groups at baseline (0.65 IU/kg for breakfast, 0.65 IU/kg for dinner, and 0.66 IU/kg for bedtime) and continued to be consistent throughout the study. All patients had similar reductions in HbA1c (7.6 –7.4% for breakfast, 7.6 –7.5% for dinner, and 7.6–7.5% for bedtime). Patients' 24 hour blood glucose levels were similar between all 3 groups. Overall rates of hypoglycemia were not different between groups, however rates of nocturnal hypoglycemia were significantly less in those who received insulin glargine before breakfast (59.5% for breakfast, 71.9% for dinner, and 77.5% for bedtime, p=0.005). This study showed the feasibility of insulin glargine either before breakfast, before dinner, or at bedtime.

In 2004, Albright et al. studied 82 patients with type 1 diabetes over a period of 12 to 15 months after switching from twice daily insulin NPH to insulin glargine.[8] This prospective, nonrandomized study had patients monitor their blood glucose 3 to 5 times daily, monitored patients' HbA1c every 8 weeks, and followed patients for 12 to 15 months. This study aimed to determine the efficacy of switching patients from twice daily insulin NPH to insulin glargine. Initially, patients were started on once daily insulin glargine. Patients that were unable to control afternoon blood glucose from titrations of basal and bolus insulin or those that experienced hypoglycemia with these titrations were then converted to twice daily dosing of insulin glargine. Twice daily insulin glargine was required in 20 patients (24.2%) and was started after a median of 259 days on once daily insulin glargine. Compared to the patients on once daily dosing versus twice daily dosing of insulin glargine there were no differences in age, baseline HbA1c, duration of diabetes, presence of detectable C-peptide, or the presence of microvascular and macrovascular complications. Significant reductions in HbA1c were achieved in both groups. The most significant drop in HbA1c was seen in patients who transitioned to twice daily insulin glargine (decrease in HbA1c from 8.1% to 7.4%, p=0.001). Those patients who stayed on a once daily regimen of insulin glargine experienced an HbA1c drop from 7.8% to 7.3%, p=0.01. Overall, about 25% of the patients required insulin glargine twice daily in order to achieve appropriate blood glucose goals. The patients who were on twice daily dosing required an average of 70% more insulin glargine (44 ± 26 units versus 26 ± 13 units, respectively; p>0.008).

In 2006, Ashwell et al. compared the glycemic effects of twice daily dosing of insulin glargine versus a once daily regimen in 20 patients with type 1 diabetes.[9] This was a single center, open-label, randomized, two-way cross-over study where each patient was on each regimen for a period of 4 weeks. Additionally, patients were on pre-prandial insulin aspart and had similar nutritional intake between 4 week treatment periods. To be included in the study patients had to be on multiple doses of insulin for at

Table 1 | Comparison of the Current Literature for Twice-Daily Dosing of Insulin Glargine

Literature	Study Type	Inclusion Criteria	Exclusion Criteria	Patient Population	Results
Heise et al.[6]	Pharmacokinetic; open, uncontrolled	• Type 1 DM for > 1 year • NPH twice daily or continuous insulin infusion • HbA1c < 8.5% • Max total insulin dose of 1 IU/kg/day	• History of hypoglycemia unawareness • Severe hypoglycemia • Treatment with BB or systemic steroids • Impaired renal or hepatic function	• 15 patients • Mean age 36 ± 9 years • 11 male, 4 female • BMI 24.6 ± 2.2 kg/m2 • Mean DM duration 17 ± 8 years	• No accumulation of insulin glargine dosed at 24 units • Mean free serum insulin levels were similar on days 1, 4, and 11
Hamann et al.[7]	Open-label, randomized, parallel group, multicenter study	• Type 1 DM • Basal-bolus therapy ≥ last 6 months • HbA1c 5.5-9.8%	• <18 years • >68 years	• 378 patients • Age 40.9 ± 11.9 years • DM duration 17.3 ± 11.5 years	• Pre-breakfast, pre-dinner, and at bedtime dosing: similar reductions in HbA1c and similar 24-hour blood glucose levels • Nocturnal hypoglycemia rates significantly less with insulin glargine pre-breakfast
Albright et al.[8]	Prospective, nonrandomized study	• Type 1 DM • NPH twice daily	• Not on NPH insulin	• 82 patients	• Most significant drop in HbA1c seen in patients who transitioned to twice-daily insulin glargine, though also required 70% more insulin glargine
Ashwell et al.[9]	Single-center, open, randomized, two-way cross-over	• Type 1 DM • Multiple insulin injection regimen for ≥1 year • Random C-peptide concentration ≤0.18 nmol/l • HbA1c 6-9.5%	• Proliferative retinopathy • Recurrent severe hypoglycemia • Impaired hepatic or renal function • Working night shifts	• 20 patients, 12 males • Mean age 43.4 ± 13.7 years • BMI 26.7 ± 4.5 kg/m2 • Baseline HbA1c 8 ± 0.9% • Mean DM duration 26.9 ± 12.1 years	• Twice-daily insulin glargine led to lower mean 24-hour blood glucose concentration and lower daily variability in blood glucose concentrations • Severe hypoglycemia occurred in 3 patients on once-daily vs 0 on twice-daily
Burge et al.[10]	Prospective, randomized, cross-over study	• Type 1 DM for >1 year • Age 18-50 years • HbA1c <9% • Basal-bolus therapy using insulin glargine	• Hospitalization within the last 12 months • Allergy to insulin glargine • Renal or hepatic impairment • NYHA class III/IV • BP >180/110 mmHg • Alcohol/drug abuse	• 10 patients, 90% female • Mean age of 40 ± 8 years • Mean DM duration 16 ± 10 years • Mean BMI of 31 ± 8 m/kg^2	• Post 24-hour study period, insulin levels were similar between once vs twice-daily insulin glargine; levels were also similar during the last four hours of the 24-hour study period • Plasma glucose concentrations pre-breakfast and pre-dinner were similar between once-daily dosing and twice-daily dosing
Hopkinson et al.[11]	Retrospective	• Type 1 diabetes	• Pregnancy • Use of continuous subcutaneous insulin infusion • Lack of HbA1c	• 892 patients, 47% male • Mean age 41 years • Mean DM duration 18.9 years • 82.8% with HbA1c ≥7.5% • 42.4% once-daily and 5.6% twice-daily	• Patients with basal insulin regimen changed from once to twice-daily had lower mean HbA1c at 12 months • Estimated RR of severe hypoglycemia with basal insulin twice daily compared to once daily dosing was 1.85 (p=0.049)

BB = beta blocker; **BMI** = body mass index; **BP** = blood pressure; **DM** = diabetes mellitus; **HbA1c** = hemoglobin A1c; **NYHA** = New York Heart Association; **RR** = relative risk

least 1 year, have a random C-peptide concentration ≤0.18 nmol/l, and HbA1c between 6% and 9.5%. Patients were excluded if they had a history of recurrent severe hypoglycemia, impaired hepatic or renal function, or if they worked night shifts. Twelve patients were male and the mean age was 43 years. Patients had a mean baseline HbA1c of 8 ± 0.9%. Patients were asked to test blood glucose at least once weekly before breakfast and encouraged to test before each meal and before bedtime daily. Patients were all given the Medisense Optimum® to monitor their blood glucose. Patients were seen at the study site once a week to asses for episodes of hypoglycemia and for titration of their insulin glargine and insulin aspart. Total units of insulin used in each regimen were similar among patients. About 25 units were given to those dosed daily in the evening while about a total of 26 units were divided between morning and evening doses in those in the twice daily group. Total units of rapid acting insulin aspart were similar between both groups (approximately 25 units). Blood glucose concentrations in patients who were dosed twice daily were found to be lower after breakfast, after lunch, and before dinner compared to those who received once daily dosing (120 versus 167 mg/dl, p=0.003; 126 versus 183 mg/dl, p=0.024; 118 versus 172 mg/dl, p=0.001; respectively). Twice daily dosing of insulin glargine led to lower mean 24 hour blood glucose concentration (127 versus 158 mg/dl, p=0.031). Additionally, with-in day variability in blood glucose was lower in patients on the twice daily regimen (57 versus 72 mg/dl, p=0.044). Overall episodes of hypoglycemia were similar between once and twice daily dosing schedules (199 versus 197 episodes). Additionally, there was no significant difference in episodes of nocturnal hypoglycemia (11 episodes in the twice daily versus 19 episodes on in the once daily). There were 3 episodes of severe hypoglycemia in those on once daily dosing, whereas no one who was dosed twice daily had any severe hypoglycemic episodes.

In 2012, Burge et al. conducted a prospective, randomized, cross-over study to determine whether twice daily dosing of insulin glargine would provide higher insulin concentrations during the last four hours of a 24-hour period compared to once daily dosing.[10] This study was performed in 10 patients (9 female) with type 1 diabetes at a mean age of 40 years. Patients were included if they presented with at least a 1 year history of type 1 diabetes, had an HbA1c < 9%, and on basal-bolus therapy using insulin glargine. Patients were excluded if they had been hospitalized within the last 12 months, had renal or hepatic impairment, or NYHA class III or IV heart disease. Insulin glargine was titrated until fasting blood glucose was <150 mg/dl. After patients were on the same dose for 1 week they were admitted to a single center where they were studied overnight. Patients fasted and received no bolus insulin during this time. Patients continued their regularly scheduled regimen of insulin glargine. Blood glucose was measured every 1 hour except during the last 4 hours of the study period when they were measured every 30 minutes. Afterwards, patients were switched to the other dosing regimen. After the 24-hour study period, insulin levels were similar between once versus twice daily dosing of insulin glargine (70 ± 56 pmol/l vs. 84 ± 63 pmol/l, p = 0.60). This was also true during the last four hours of the 24-hour study period as once daily and twice daily dosing of insulin glargine had similar insulin concentrations, p=0.38. Additionally, patients recorded their plasma glucose concentrations before breakfast during the week prior to the in-patient study, which found no significant difference between once daily dosing and twice daily dosing (174 ± 74 mg/dl vs. 168 ± 72 mg/dl, respectively; p = 0.64). This was also true for plasma glucose concentrations measured before supper (169 ± 92 mg/dl vs. 191 ± 104 mg/dl, respectively; p = 0.27). These results suggest that there appears to be a lack of additional benefit for twice daily dosing of insulin glargine compared to once daily dosing among patients with type 1 diabetes. A limitation of this study is that the total daily insulin requirement for these patients was not noted; therefore it is uncertain if with increasing total daily units of insulin that a difference would have been observed between the two dosing regimens.

In 2015, Hopkinson et al. studied the relationship between basal insulin regimen and glycemic outcomes in patients with type 1 diabetes.[11] These patients were provided with education on how to dose adjust their insulin and were followed up after 12 months. This retrospective study included 892 patients (47% male) with a mean age of 41 years and mean duration of diabetes 18 years. Baseline HbA1c was ≥ 7.5% in 82.8% of patients. Patients were excluded for the following reasons: pregnancy, use of continuous subcutaneous insulin infusion, and lack of baseline HbA1c values. Various basal insulins were used in the study, which included NPH, insulin glargine, and insulin detemir. At baseline 48% of the patients used insulin glargine (42.4% dosed daily, 5.6% dosed twice daily). After 12 months, 42% of patients used insulin glargine (30.3% dosed daily, 11.7% dosed twice daily). Overall, there was no difference in 12 month HbA_{1c} between the different basal insulins, p=0.337. Patients who had their basal insulin regimen (insulin glargine, detemir, or NPH) changed from once to twice daily had lower mean HbA_{1c} at 12 months with an average drop in HbA_{1c} of 0.3% (p<0.001) while those patients that remained on once daily basal insulin regimens had a mean HbA1c drop of 0.1% (p=0.222). For patients with a baseline HbA1c ≥7.5%, twice daily dosing of basal insulin continued to have a greater reduction in HbA1c than once daily dosing, which ob-

Table 2 | Comparison of Insulin Glargine Formulations

Brand	Concentration	Onset of Action	Duration of Action	Conversion to Lantus®	Conversion to Basaglar®	Conversion to Toujeo®
Lantus®	100 units/ml	~1.5 hours	Up to 24 hours	---	1:1	1:1
Basaglar®	100 units/ml	Max concentration 12 hours post-injection	Up to 24 hours	1:1	---	1:1
Toujeo®	300 units/ml	~6 hours, full effect may take up to 5 days	Up to 36 hours	1:0.8	1:0.8	---

served a decrease of 0.4% (p<0.001) versus 0.2% (p=0.011) respectively. The estimated relative risk of severe hypoglycemia with basal insulin dosed twice daily compared to once daily dosing was 1.85 (p=0.049). There was also no difference in the rates of severe hypoglycemia between the three types of insulin. While this study focused on once versus twice daily basal insulin regimens, it does not clearly provide analysis of those patients on insulin glargine as it included patients on NPH and insulin detemir in its analysis. Hence, the superiority of insulin glargine dosed twice daily over once daily is unclear in this study.

Dosing and Administration

Insulin glargine is currently available as Lantus® (100 units/ml), Basaglar® (100 units/ml), and Toujeo® (300 units/ml). **Table 2** provides a comparison between the different insulin glargine formulations. These pens all provide up to 80 units for a single injection; hence patients requiring more than 80 units will need to administer at least 2 injections to reach their prescribed dose. This may lead to issues with compliance as many patients are already adverse to one injection daily. Additionally, if insulin glargine were dosed twice-daily, then some patients would need at least four injections daily. With this split dosing regimen, patients could potentially forget to take their second injection later in the day.

Conversion from Lantus® to Basaglar® is a 1:1 ratio; hence, the dose will be the same between these products. When changing from Lantus® to Toujeo®, it should be expected that a higher dose of Toujeo® will be necessary. In trials, Toujeo® dose requirements were 11% to 17.5% higher than for Lantus®.[12] When changing from Toujeo® to Lantus®, 80% of the Toujeo® dose should be initiated.

Conclusion

In summary, the current available evidence for insulin glargine dosed once versus twice daily has only been studied in patients with type 1 diabetes. This raises questions as to whether this literature can be applied to those patients with type 2 diabetes. For patients that experience nocturnal hypoglycemia, insulin glargine may be dosed before breakfast especially in those patients only on basal insulin who are reluctant to start twice daily injections. Otherwise, twice daily administration of insulin glargine would be an appropriate regimen to circumvent nocturnal hypoglycemia. Twice daily dosing of insulin glargine has also been shown by some studies to significantly lower blood glucose concentrations throughout the day as well as lower daily blood glucose variability. Twice daily dosing of insulin glargine has also been shown to be effective in patients with persistent elevations of afternoon blood glucose despite titrations of insulin glargine and bolus insulin. Additionally, there have been concerns as to whether after a certain dose of insulin glargine has been reached that the body will not be able to adequately absorb that amount with one subcutaneous injection. Currently, this has been studied up to 25 units of insulin glargine which has been found to be safely and effectively absorbed at this dose. Further studies are needed to determine at what dose, if any, insulin glargine should be administered twice daily due to issues with subcutaneous absorption.

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Personalized Medicine Corner

New Clinical Outcomes Support Pharmacogenetic-Guided Warfarin Therapy

Warfarin is an anticoagulant prescribed for prophylaxis and treatment of thromboembolic disorders.[1] There is significant interpatient variability in warfarin dose requirements, which is attributed to clinical (e.g. age, body size, concomitant medications), dietary (e.g. vitamin K intake), and genetic factors. The primary genes influencing warfarin dose requirements are *CYP2C9,* which encodes for the primary metabolizing enzyme of *S*-warfarin, and *VKORC1*, which encodes for the protein target of warfarin. Previous trials of genotype-guided warfarin dosing that focused on a primary endpoint of time in therapeutic range have yielded inconsistent results. Findings from the first trial powered to detect clinical outcomes, Genetics InFormatics Trial (GIFT), were presented at the American College of Cardiology meeting in March 2017.[2,3]

GIFT included 1,597 patients (64% female, 91% Caucasian) age 65 years or older who underwent hip or knee arthroplasty and were initiated on warfarin for venous thromboembolism (VTE) prophylaxis. Patients were randomized to warfarin dosing with a pharmacogenetic algorithm, including both genotype and clinical factors, or clinical algorithm, including clinical factors only. A web application (warfarindosing.org) provided recommendations for the first 11 days of therapy followed by standard of care adjustments using International Normalized Ratio (INR) results. There was a lower rate of the composite outcome of VTE, major hemorrhage, INR $\geq$4, or death with pharmacogenetic versus clinical dosing (10.8% vs. 14.7%; relative risk= 0.73; 95% confidence interval, 0.56-0.95). The full manuscript for the trial is not yet published.

The process for implementing warfarin pharmacogenetics into practice has been described, and guidelines are available by the Clinical Pharmacogenetics Implementation Consortium to assist with interpretation and translation of genotype data to warfarin dosing decisions.[4,5] For questions on ordering and interpreting a pharmacogenomic test, contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu) .

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