

TABLE OF CONTENTS

• Intensive Glycemic Control and Cardiovascular Events: An Update	1-3
• The Utilization of Pharmacogenomics in Clinical Practice	3-4
• Dalteparin Use Guideline	4-6
• P&T Committee Formulary Action	6

Intensive glycemic control and cardiovascular events: an update

VA Diabetes Trial

The question of whether intensive glycemic control in patients with type 2 diabetes reduces cardiovascular disease (CVD) events was evaluated in the Veterans Affairs Diabetes Trial (VADT), which was similar to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials. The VADT was a randomized, controlled, open-label study which included patients who were 41 years or older with a glycated hemoglobin (A1C) level $\geq 7.5\%$ on a maximum dose of at least 1 oral agent and/or daily insulin injections. Selected exclusion criteria were renal or liver dysfunction, a CVD event within the past 6 months, Class III or IV angina or heart failure, and life expectancy less than 8 years. Of 1791 patients, 892 were randomized to intensive treatment and 899 to standard treatment and stratified according to study site, previous occurrence of a CVD event, and current insulin use. The trial had a 2-year data accrual period and a 5-year follow-up period. The target A1C for intensive treatment was to achieve an absolute difference of 1.5 percentage points from the standard treatment group ($\leq 6\%$ for the intensive group; 8% to 9% for the standard group). All patients entering the intensive treatment group on oral agents alone received rosiglitazone 4 mg twice daily and maximum doses of either metformin or glimepiride depending on their body mass index (BMI); obese patients who had a BMI of 27 mg/m² or greater received metformin, and those with a lower BMI received glimepiride. Insulin was added to the oral regimen if necessary. Patients entering the intensive treatment group already on insulin had their regimens intensified to achieve the desired targets. Patients in the standard treatment group received similar oral and/or insulin drug therapy as the intensively treated patients; however, lower doses were used. Both treatment groups had other cardiovascular risk factors managed according

to guidelines, which included a blood pressure goal of < 130/80 mm Hg, low density lipoprotein (LDL) goal of < 100 mg/dL and triglyceride (TG) goal of < 200 mg/dL, use of low dose aspirin (81 to 325 mg), and counseling on lifestyle modification and smoking cessation. The primary outcome was the time to first occurrence of a CVD event which included myocardial infarction (MI), stroke, death from cardiovascular causes, new or worsening heart failure, surgical intervention for cardiac, cerebrovascular or peripheral vascular disease, inoperable coronary artery disease, and amputation for ischemic gangrene. Microvascular complications and other cardiovascular events were the secondary outcomes.

Results

As would be expected in a veteran population, approximately 97% of patients were male. The mean age of patients was 60.4 years with a mean duration of diabetes of 11.5 years and a mean BMI of 31.3 mg/m². Mean baseline A1C was 9.4%, and 52% of patients were receiving insulin at baseline. At the end of follow-up (mean duration of 6 years), both groups achieved goal mean blood pressure, LDL, and TG levels. Glycated hemoglobin values stabilized after 6 months of therapy at a median level of 6.9% in the intensive group and 8.4% in the standard group. Aspirin use increased similarly in both groups, as did smoking cessation. Compared to standard treatment, intensive treatment led to statistically significant increases in mean body weight (223 lbs vs. 232 lbs, $p=0.01$) and mean BMI (32.3 kg/m² vs. 33.8 kg/m², $p=0.01$).

No statistically significant difference was observed in the 6-year event rate of the primary outcome between the intensive treatment group (0.66) and the standard treatment group (0.70) (hazard ratio 0.88; 95% confidence interval [CI], 0.74 to 1.05; $p=0.14$). Two hundred sixty four events occurred in the standard group compared to 235 events in the intensive group. Use of insulin at baseline or a previous CVD event did not influence the outcome of either

treatment. The only microvascular outcome that improved with intensive treatment compared to standard treatment was worsening of albumin excretion ($p=0.05$). Although not statistically significant, there were a greater number of cardiovascular deaths in the intensive group compared to the standard group (40 vs. 30, respectively) and a greater number of sudden deaths (11 vs. 4, respectively). Hypoglycemia occurred more frequently with intensive treatment and was documented as a serious adverse event in 76 (8.5%) of 892 intensively treated patients compared to 28 (3.1%) of 899 patients receiving standard treatment ($p=0.000$). Dyspnea occurred significantly more frequently with intensive treatment compared to standard treatment (11% vs. 7.2%, respectively, $p=0.006$).

Discussion

In the ACCORD trial, the composite primary endpoint of macrovascular events was not significantly different between the intensive and standard treatment groups. In fact, death from CVD or any cause was significantly higher in the intensive group, which led to early termination of the trial. In the ADVANCE trial, the composite primary endpoint of macrovascular and microvascular events was significantly lower in the intensive control group compared to the standard control group. When evaluated separately, the main reason for the reduction in the primary endpoint was the decrease in microvascular events, particularly new or worsening nephropathy, in the intensive therapy group.

Similar to results of the recently conducted ACCORD and ADVANCE trials, intensive treatment of type 2 diabetes in the VADT did not lead to a significant reduction in CVD events compared to standard treatment. Although the ACCORD trial was terminated early due to an increase in mortality with intensive treatment, a subgroup analysis of intensively treated patients with no previous CVD events and a baseline A1C of $< 8\%$ demonstrated significant reduction in CVD events. Post hoc analyses of the VADT results have also suggested lower CVD events in patients with a shorter duration of diabetes at randomization. Additionally, for patients receiving standard treatment, previous hypoglycemic episodes appeared to be associated with increased mortality.

Two older, pivotal trials, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) also compared microvascular and CVD outcomes of intensive treatment of type 1 and newly diagnosed type 2 diabetes, respectively. After an average duration of 6.5 years, intensive treatment of type 1 diabetes (average A1C of 7.2%) in the DCCT led to a 60% reduction in retinopathy, nephropathy, and neuropathy, but no significant difference in cardiovascular events. However, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, a follow up study of DCCT patients 10 years after treatment groups reached similar A1C levels, demonstrated a 57% reduction in nonfatal MI, stroke, or CVD related death in patients who had previously received intensive treatment compared to those who had received standard treatment ($p=0.02$). In

type 2 diabetes, intensive treatment (median A1C of 7%) for an average of 10 years in the UKPDS study led to a 25% reduction in the overall microvascular complication rate and a nonsignificant 16% decrease in cardiovascular events. A 10-year follow up study of UKPDS patients demonstrated a 15% reduction in MI ($p=0.01$) for patients who received previous intensive glycemic control with a sulfonylurea or insulin as initial therapy and a 33% reduction in MI ($p=0.005$) for patients with previous intensive control with metformin as initial therapy compared to those who received conventional treatment.

Recommendations

Based on the results of these various studies, the American Diabetes Association (ADA), in conjunction with the American Heart Association (AHA) and the American College of Cardiology (ACC), has published a position statement on intensive glycemic control and CVD events. According to the statement intensive glycemic control early in the course of diabetes in patients without established CVD can help to reduce future CVD events. Intensive glycemic control in advanced diabetes and established CVD, on the other hand, may not play a role in prevention of future CVD events.

The statement provides the following guidelines for clinical practice:

- An A1C goal of $< 7\%$ to prevent microvascular complications in patients with type 1 and type 2 diabetes. A lower goal closer to normal, if achievable without significant hypoglycemia, may be set for patients with a short duration of diabetes, long life expectancy, and no previous CVD.
- An A1C goal of $< 7\%$ early in the course of the disease to prevent macrovascular complications in patients with type 1 and type 2 diabetes.
- An A1C goal $> 7\%$ should be considered in patients with advanced age, advanced microvascular or macrovascular disease, significant hypoglycemia, limited life expectancy, and severe comorbid conditions.

These guidelines differ from previous recommendations in that specific populations have been identified in which intensive glycemic therapy may be beneficial or potentially harmful in terms of prevention of macrovascular disease. The recommendations, similar to previous guidelines, continue to support management of other CVD risk factors such as blood pressure, cholesterol, smoking cessation, and use of antiplatelet therapy as the primary means to reduce CVD risk in patients with diabetes.

Clinicians should strive for intensive glycemic control early in the course of diabetes to prevent microvascular and macrovascular complications. However, intensive glycemic control may be less beneficial and potentially harmful in patients with long standing diabetes, significant hypoglycemia, and other serious comorbidities.

The utilization of pharmacogenomics in clinical practice

The field of pharmacogenomics is certainly not a new one. It has been evolving for the past 50 years but has become more mainstream due largely in part to the completion of the Human Genome Project in 2003. With the development of new molecular technology and the sequencing of human DNA, pharmacogenomics has reemerged. A goal of this research is to tailor drug therapy based on the genetic makeup of the patient while minimizing the risk of adverse effects. Researchers have identified genetic variations that are associated with adverse effects and the clinical response of drugs. As a result, there are several genetic tests for specific medications that can be used to predetermine therapeutic efficacy or the risk of adverse effects.

TPMT Testing

Azathioprine, an immunosuppressive agent, is metabolized to 6-mercaptopurine (6-MP). The thiopurine s-methyltransferase (TPMT) enzyme inactivates 6-MP via 1 of 3 metabolic pathways. Some patients have a TPMT deficiency, resulting in higher concentrations of the active drug and dose-limiting adverse effects such as leukopenia, anemia, and thrombocytopenia. An estimated 10% of patients (Caucasians and African Americans) have 1 functional and 1 non-functional TPMT allele. Approximately 0.3% of patients have little or no TPMT activity due to the presence of 2 non-functional alleles. Anasari and colleagues found that 15 of 19 (79%) patients with a heterozygous TPMT genotype discontinued azathioprine treatment due to adverse effects compared to 66 of 188 (35%) patients with TPMT wild type ($p=0.000265$). Gastrointestinal (GI) intolerance and myelotoxicity were more common in the heterozygous TPMT group compared to the TPMT wild type group ($p<0.001$ and $p<0.01$, respectively). According to the prescribing information of azathioprine and 6-MP, TPMT testing should be considered, and dose reductions are recommended in patients with TPMT deficiency.

UGT1A1 Testing

Irinotecan, a topoisomerase inhibitor, is associated with toxicities (diarrhea and neutropenia). These drug-limiting adverse effects are thought to be related to uridine diphosphate glucuronosyltransferase (UGT) enzymes which play a role in the metabolism of irinotecan. Irinotecan is a prodrug that is metabolized to an active compound, 7-ethyl-10-hydroxycamptothecin (SN-38). The inactivation of SN-38 is catalyzed by UGTs. In a meta-analysis of 9 studies comprising 821 patients, the risk of hematologic toxicity was higher at medium (150 to 250 mg/m²) and high (> 250 mg/m²) doses of irinotecan in patients with the UGT1A1*28/*28 allele than those patients with 1 or 2 wild-type alleles, UGT1A1*1/*1 or UGT1A1*1/*28, ($p=0.008$ and $p=0.005$, respectively). No significant difference was shown

at low doses between either genotype. In 2005, changes to the prescribing information of irinotecan were made to include the recommendation of a lower initial dose for patients with a homozygous UGT1A1*28 allele. Also, the Food and Drug Administration (FDA) approved the Invader UGT1A1 Molecular Assay for detecting the *1 and *28 alleles of the UGT1A1 gene. However, neither the current labeling for the drug or the National Comprehensive Cancer Network recommend patients get tested for the presence of UGT1A1 alleles prior to irinotecan treatment.

HLA-B*1502 Testing

Carbamazepine (CBZ), an antiepileptic drug, can cause serious skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). A specific human leukocyte antigen (HLA) allele, HLA-B*1502, has been implicated as a predictor of CBZ-induced SJS and TEN. Patients of the Asian descent who are exposed to CBZ are at a higher risk of developing SJS or TEN due to HLA-B*1502 being more prevalent compared to other ethnic groups. In addition, patients with the HLA-B*1502 allele may be at increased risk of SJS/TEN while taking other antiepileptic drugs that can also cause these severe skin reactions. A small study of 31 Thai patients with epilepsy found that all patients ($n=10$) who tested positive for HLA-B*1502 experienced CBZ or phenytoin-induced SJS/TEN. The FDA currently recommends patients of Asian descent be tested for the HLA-B*1502 allele prior to initiating therapy with CBZ. If they test positive, it is suggested to consider antiepileptic therapy not associated with SJS/TEN. While a negative result does dramatically reduce the risk of developing SJS reactions, the risk is not completely eliminated. Therefore, during the first few months of therapy, patients should be closely watched for presentations of adverse events.

HLA-B*5701 Testing

The latest guidelines on the use of antiretroviral agents in human immunodeficiency virus type 1 (HIV-1) patients recommend HLA-B*5701 testing for all patients who are to be started on abacavir, a nucleoside reverse transcriptase inhibitor. Abacavir is associated with hypersensitivity reactions, including 2 or more of the following symptoms: rash, fever, fatigue, gastrointestinal intolerance, and respiratory symptoms (pharyngitis, dyspnea, or cough). Life-threatening events including hypotension and death have also occurred. It is recommended not to re-challenge patients with abacavir if these reactions occur, and to report adverse events to the manufacturer or to the FDA via the MedWatch Adverse Event Reporting program (www.fda.gov/medwatch/report.htm). Studies have shown a strong correlation between those patients who test positive for the HLA B*5701 allele and the risk of developing hypersensitivity reactions. However, testing positive for the HLA-B*5701 allele does not guarantee a patient will react negatively to the drug.

VKORC1/CYP2C9 Testing

A current clinical controversy involves whether genetic testing should be done in patients starting warfarin. The

cytochrome P-450 isoenzyme 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 (VKORC1) genes have been implicated in determining a patient's sensitivity to the anticoagulant. Due to these findings, the prescribing information was revised to include the effect of genetic variations on a patient's response to warfarin and appropriate dosing and monitoring. Patients who have CYP2C9 polymorphisms are less likely to metabolize the active S-isomer of warfarin, leading to increased drug levels and higher risk of bleeding. These patients have been shown to require lower total doses of warfarin. Genetic variations in VKORC1 can cause increased sensitivity or resistance to warfarin due to deficient vitamin-K clotting factors. It has been shown that VKORC1 and CYP2C9 variations, along with environmental and clinical factors, account for 20.4% to 56% of warfarin dose variability. However, genetic testing prior to the initiation of warfarin is not currently recommended by the American College of Chest Physicians due to the lack of well designed clinical trials. In addition, there are also cost concerns. The International Warfarin Pharmacogenetics Consortium found that a pharmacogenetic algorithm based on genetic and clinical variables provided more accurate dose estimates for warfarin than the clinical algorithm (included only clinical variables) and a fixed-dose approach; 35% of the dose predictions fell within 20% of the actual dose ("ideal dose") with the pharmacogenetic algorithm as compared with 24% with the clinical algorithm and 0% with the fixed-dose approach ($p < 0.001$ for both comparisons).

The ability to individualize a patient's therapy based on their genetic makeup seems to be more promising due to pharmacogenetics. However, there are some barriers to overcome such as ethical concerns and the lack of quality clinical and economic data. This article highlights a few of the pharmacogenetic tests available. Recently in the news the FDA has initiated an investigation into whether patients' response to clopidogrel can be genetically determined due to the reports of inconsistent efficacy amongst patients. Clopidogrel is an inactive compound that requires metabolism to its active state. Studies have associated the reduced anti-platelet activity of clopidogrel with genetic variations, a deficient CYP2C19 allele. Visit www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm for additional information.

The field of pharmacogenomics is constantly evolving as more genetic variations are being linked to the safety and efficacy of drugs. Currently, only a few genetic tests are being routinely used in clinical practice. Testing for the presence of the HLA-B*5701 allele should be used in clinical practice as the guidelines recommend that all HIV patients be tested before the initiation of abacavir. In addition, epileptic patients of the Asian descent should be screened for the presence of HLA-B*1502 allele before starting CBZ therapy. In the future, genetic testing will play a more intricate role in clinical practice.

Dalteparin Use Guideline

Dalteparin is the low molecular weight heparin (LMWH) on the UIMCC Formulary for which a clinical care guideline has been developed. Clinicians are referred to UIMCC intranet to access and review the full guideline ([G-13.22 Dalteparin Use in Adults](#)). Below is a summary of key points from the guideline.

Clinical indications for dalteparin

Food and Drug Administration (FDA)-approved indications:

- Prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery and in patients who are at risk for thromboembolic complications when undergoing abdominal surgery or medical patients with restricted mobility
- Extended treatment of symptomatic venous thromboembolism (VTE) such as proximal DVT and/or PE to reduce the recurrence of VTE in patients with cancer
- Prophylaxis of ischemic conditions (acute coronary syndrome) in patients with unstable angina and non-Q wave myocardial infarction (NQWMI), given concomitantly with aspirin

Other clinical indications but not FDA-approved:

- Treatment of VTE (acute symptomatic DVT and/or PE)
- Bridging therapy for patients being transitioned to warfarin or for peri-procedure bridging for patients who require interruption of chronic warfarin therapy for invasive procedures or surgical intervention

Dalteparin dosing

Tables 1 and 2 describe dalteparin dosing for prophylaxis and treatment clinical indications.

Administration

Dalteparin is administered by deep subcutaneous injection in the U-shaped area around the navel (abdomen), the upper outer side of the thigh, or the upper outer side of the buttock. The injection site should vary daily. Steps for administration are as follows:

1. DO NOT expel the air bubble from the syringe before injection.
2. Using the thumb and forefinger, you must lift up a fold of skin while giving the injection around the navel or in the thigh.
3. The entire length of the needle should be inserted at a 45 to 90 degree angle.
4. After completing administration, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle with a "click" sound. The safety system can only be activated once the syringe has been emptied.
5. DO NOT rub the injection site after the administration of dalteparin.

Table 1. Dalteparin prophylaxis doses.

Indication/Use	Dalteparin Dose
Prophylaxis of DVT, which may lead to PE	
Orthopedic surgery • Hip replacement surgery • Knee replacement surgery	2,500 units SC 4 to 8 hours after surgery, followed by 5,000 units SC every 24 hours
Abdominal surgery	5,000 units SC the evening prior to surgery then 5,000 units SC once daily postoperatively in patients at high risk of thromboembolic complications OR 2,500 units SC 1 to 2 hours prior to surgery followed by 2,500 units SC 12 hours later then 5,000 units SC once daily postoperatively in patients with malignancy
Medical patients • With restricted mobility during acute illness	5,000 units SC once daily

Table 2. Dalteparin treatment doses.

Indication/Use	Dalteparin Dose
Treatment of Venous Thromboembolism	
Acute DVT with or without PE • Initial acute phase therapy	200 units/kg SC every 24 hours (in conjunction with warfarin therapy; given for a minimum of 5 days and until the INR > 2 and stable)
Extended treatment of DVT and/or PE in patients with cancer	1 st month of therapy: 200 units/kg SC every 24 hours 2 nd to 6 th month of therapy: 150 units/kg SC every 24 hours
Bridging therapy • Bridging to therapeutic INR or peri-procedure during prolonged periods of under-anticoagulation	200 units/kg SC every 24 hours
Acute coronary syndromes • Prophylaxis of ischemic complications in unstable angina and NQWMI, when concurrently administered with aspirin	120 units/kg SC every 12 hours with concurrent aspirin therapy

DVT=deep vein thrombosis; PE=pulmonary embolism;
 SC=subcutaneous; kg=kilogram;
 INR=international normalized ratio; NQWMI= non-Q wave myocardial infarction

Monitoring parameters

Orders will be verified and filled by pharmacy if there is a pending request for the baseline laboratory tests to be drawn within 24 hours of the initial dalteparin dose. Requirements are provided in the table below.

- Baseline is defined as lab results obtained within 7 days prior to initiation of dalteparin
- Current weight is defined as within 7 days of initiation
- Current height is defined as within 1 year of initiation

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Monitoring Parameter	Requirements
CBC with platelet count	Baseline and at least every 3 days as long as patient is on therapy or up to Day 14, whichever is sooner
Serum creatinine and creatinine clearance	Baseline and current (at least every 7 days)
Weight	Current
Height	Current

CBC=complete blood count

Pharmacy procedure

Inpatient and outpatient screening before dispensing a new dalteparin prescription will include pharmacists' review. The screening process will include a baseline creatinine clearance and a complete blood count with platelet count.

The clinical care guideline has information on dose rounding, dose adjustment in special populations (obesity, pediatrics, pregnancy, renal impairment, and spinal or epidural analgesia), as well as information on monitoring anti-factor Xa activity, which is not routinely recommended. The clinician should refer to the complete guideline for further information.

P&T Committee Formulary Action

Additions

- Dalteparin injection

Deletions

- Enoxaparin injection
- Benzoic acid/salicylic acid topical
- Tincture of benzoin compound topical
- Dorzolamide/timolol 2%-0.5% ophthalmic solution
- Papain urea topical ointment (Accuzyme)
- Papain urea chlorophyllin copper complex sodium topical spray (Panafil SE)