A 67-year-old man presents for ongoing management of his cardiometabolic health. He has had type 2 diabetes mellitus (T2DM) for 7 years, hypertension, and dyslipidemia; is overweight; and suffered an inferior myocardial infarction 2 years earlier. Under your advice, he has made attempts to exercise with 30 minutes of daily walking and has tried to make healthy dietary choices and to watch food portion sizes. Over the past year, he lost 7 kg but regained 4 kg and remains overweight. His medications include metformin, a statin, an angiotensin-converting enzyme inhibitor, a β-blocker, and low-dose aspirin.

On examination, his weight is 91.5 kg, body mass index is 32.0 kg/m², waist circumference is 105.3 cm, and blood pressure 138/84 mm Hg. The rest of the examination is unremarkable and shows no evidence of microvascular complications of diabetes mellitus.

His fasting plasma glucose is 10.3 mmol/L (185 mg/dL) and hemoglobin A₁c (HbA₁c) is 7.9%.

Screening for Prediabetes and Diabetes Mellitus
Atherosclerosis is the principal cause of death and disability in patients with T2DM. In these patients, cardiovascular disease typically occurs at an early age, with great severity and diffuse distribution. More than half of the patients with newly diagnosed T2DM have established coronary artery disease, whereas one third of patients with coronary artery disease have known diabetes mellitus. Screening patients with established coronary artery disease but without preexisting diabetes will confirm the diagnosis of diabetes mellitus in an additional 15% to 20%. Impaired fasting glucose or impaired glucose tolerance will be detected in an additional 30% to 40%. Thus, more patients with established heart disease have abnormal than normal glucose tolerance, and screening for diabetes mellitus is warranted in patients with coronary artery disease or risk factors for cardiovascular disease.

There are now multiple accepted ways to screen for diabetes mellitus in adults, including measurement of fasting plasma glucose, HbA₁c, or 2-hour plasma glucose after a 75-g oral glucose tolerance test. When abnormal, each test identifies distinct but overlapping groups of patients at high risk of progression to or early T2DM. Although the HbA₁c diagnostic cutoff point of 5.6% identifies fewer patients with undiagnosed diabetes mellitus compared with fasting or post–oral glucose tolerance test glucose, it has the advantage of wider application in that it can be performed regardless of fasting or timed samples, is largely unaffected by acute illness, and may be used to guide management and to adjust therapies.

An important caveat in using HbA₁c is that the test may not be accurate in assessing glycemic status in the presence of factors that alter red cell turnover such as hemoglobinopathies, anemia, or recent blood transfusions.

Each of these tests is acceptable for diagnosing diabetes mellitus and is considered a gold standard. However, a positive diagnostic test should be repeated for confirmation of the diagnosis unless there is unequivocal clinical evidence of diabetes mellitus such as typical symptoms or presentation with severe hyperglycemia. If 2 tests screening for diabetes mellitus are obtained and are discordant, then the test that is above the diagnostic threshold should be repeated.

Approach to Prediabetes
Patients with impaired fasting glucose (fasting plasma glucose, 5.6–6.9 mmol/L
or 100–125 mg/dL), impaired glucose tolerance (2-hour post–oral glucose tolerance test glucose, 7.8–11.0 mmol/L or 140–199 mg/dL), or HbA1c between 5.7% and 6.4% are considered to have prediabetes. Although not all patients with prediabetes will progress to overt diabetes mellitus, the rate of conversion is particularly high in this group, ≈10%/y. Many therapeutic approaches delay or prevent the progression to diabetes mellitus and are appropriate for the patient with or without established coronary artery disease. Nonpharmacological modalities, including medical nutrition therapy, physical activity, behavioral modifications, and weight loss, are summarized in Table 1. For the patient with multiple risk factors for T2DM progression or when the patient is unable to incorporate lifestyle interventions, metformin use may be appropriate, although there is some evidence to suggest that it is less effective in the older population. Metformin should not be prescribed for patients with low glomerular filtration rates. In high-risk patients with pre-diabetes, diabetes prevention through lifestyle modification or metformin has been demonstrated to be cost-effective and even cost-saving. Acarbose, an α-glucosidase inhibitor that blocks the absorption of dietary carbohydrate, has also been demonstrated to reduce the progression from impaired glucose tolerance to diabetes mellitus and may have favorable effects on cardiovascular event rates. Although thiazolidinediones (such as rosiglitazone and pioglitazone) may also prevent T2DM, their use for the prevention of diabetes mellitus is debated, in part because of weight gain and the controversial effects on cardiovascular event rates with rosiglitazone. Statins have been associated with incident T2DM, especially among those with prediabetes. However, their cardiovascular benefits are clear for secondary cardiovascular disease prevention and for patients at high risk of first events.

**Back to the Case:**

**Role of Metformin**

This patient is on metformin, which is the preferred initial pharmacological agent for the treatment of T2DM for patients with adequate renal function. Metformin, approved by the US Food and Drug Administration in 1995, has accrued long-term clinical experience, is efficacious, has established low side-effect profile, and is inexpensive. Metformin effectively lowers blood glucose over wide range of HbA1c levels without provoking hypoglycemia and is safe to initiate in the majority of patients with prediabetes or T2DM. It is weight neutral or may promote modest weight loss and has the distinction among current antihyperglycemic agents of reducing major adverse cardiac events.

Metformin is contraindicated in patients with elevated serum creatinine levels because of concerns about lactic acidosis. However, lactic acidosis is rare, and metformin is often used without adverse effects in those with mildly to moderately impaired renal function. Renal function should be closely monitored in patients with estimated glomerular filtration rates between 45 and 60 mL·min<sup>−1</sup>·1.73 m<sup>2</sup>, along with consideration of reducing the metformin dose to half, and metformin should be discontinued for those with estimated glomerular filtration rate <30 to 45 mL·min<sup>−1</sup>·1.73 m<sup>2</sup> or for those whose cardiac function may cause variable

| Table 1. Nonpharmacological Approaches for Prediabetes and T2DM |
|---------------------|----------------------|
| **Modality** | **Remarks** |
| Medical nutrition therapy | Individualized diabetes-centered nutritional counseling provided by a registered dietician can have salutary effects on weight loss, glycemic control, blood pressure, lipid profiles, and progression of complications. Empower patients to control portion sizes and make healthy food choices from macronutrients: Carbohydrates—encourage carbohydrate counting and selecting from a variety of low-glycemic-index and high-fiber foods, fruits, vegetables, whole grains, legumes, and low-fat dairy products. Fat—reduce overall dietary fat intake and consider diets enriched with monounsaturated and polyunsaturated fatty acids (Mediterranean diet), which have been associated with better cardiovascular outcomes and lowered mortality. Protein—consume more lean protein foods and recognize that protein intake may need to be reduced in those with chronic kidney disease. |
| Physical activity | Regular aerobic exercise, at least 150 min/wk spread over a minimum of 3 d (no more than 2 consecutive days without exercise), should be performed if cardiovascular health permits. When feasible, resistance training at least twice a week can improve glycemic control. |
| Behavioral modifications | Individuals require support and coping strategies for lifestyle changes, including a healthy diet, exercise, weight reduction, smoking cessation, and treatment compliance. Psychotherapy may useful in those with significant psychosocial issues and depression. |
| Weight loss | Weight reduction (aimed at 7% weight loss) is the cornerstone of treatment for overweight or obese individuals with prediabetes or T2DM. In tandem with other lifestyle modifications such as exercise and behavioral modifications, a low-carbohydrate, low-fat calorie-restricted diet may be a helpful strategy. Bariatric surgery remains an effective option for obese patients with T2DM, especially when lifestyle interventions or pharmacotherapy is unsuccessful, but cardiovascular surgical risk must be carefully considered. New FDA-approved pharmacological agents are available for weight management, although durability and longer-term safety data remain elusive. |

FDA indicates US Food and Drug Administration; and T2DM, type 2 diabetes mellitus.
or intermittent secondary severe renal insufficiency. Metformin is generally well tolerated, although gastrointestinal side effects, including a metallic taste, nausea, abdominal discomfort, and diarrhea, are the most commonly reported. These can often be overcome by initiation at a low dose followed by slow dose escalation.

**Diabetes Therapeutics: Individualization Is Key**

Glycemic targets for the patient with T2DM should be individualized. Considerations for establishing glycemic targets in patients with coronary artery disease include age, disease duration, prognosis, hypoglycemic risk, and psychosocial factors. Complications attributable to hyperglycemia take years to develop, and patients with limited life expectancy may not reap the benefits of intensive glycemic control. Nonetheless, all patients benefit from maintaining blood sugars below thresholds that lead to acute side effects of hyperglycemia, including polyuria, nocturia, polydipsia, and polyphagia, which occur commonly with average blood glucose >10.0 to 11.1 mmol/L (180–200 mg/dL) or HbA1c >8% to 9%. More stringent goals (ie, HbA1c of 6%–6.5%) further reduce the risk of microvascular complications and are appropriate for those who can easily attain near-normal glycemia safely. Although attempts to achieve near-normal glycemia were associated with increased mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, this has not been observed in other studies of intensive glycemic control.

Factors associated with persistently higher HbA1c levels despite intensive glycemic control rather than low HbA1c per se may contribute importantly to the increased mortality seen in ACCORD. A meta-analysis of randomized, controlled clinical trials showed that intensive glycemic control reduces the relative risk of nonfatal myocardial infarction and coronary artery disease events by ≈15%. Although there is no effect on all-cause mortality, it is possible that translating cardiovascular benefits into reduced mortality would require a longer study duration than provided in these trials, as supported by risk reductions for myocardial infarction and death in the long-term follow-up of the UK Prospective Diabetes Study (UKPDS). Waiting some years after the diagnosis of T2DM before tightening glycemic control might not recapture the benefits that would be realized with early intervention. The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial supports safe use of a basal insulin regimen and target of normal fasting glucose in patients with prediabetes or diabetes mellitus and cardiovascular risk factors, although there was no reduction in cardiovascular events within the time frame of the study. Thus, targeting HbA1c of <7% is appropriate for most patients with established cardiovascular disease, provided that this can be achieved safely.

**Selecting the Next Therapeutic Option**

T2DM is widely recognized to be a progressive disorder, and ongoing assessment of the need for intensification of therapy is warranted, as seen with the patient presented here. In general, HbA1c rises at ≈0.2%/y to 0.3%/y on stable oral antihyperglycemic agents, prompting the need for combination therapies. Secondary glycemic failure occurs at rates of ≈5% to 10% annually, somewhat faster with sulfonylureas, intermediate with metformin, and slowest with thiazolidinediones. The durability of the effectiveness of other classes of drugs used to treat T2DM has not been as carefully compared. Disease progression is attributed largely to increasing β-cell dysfunction but can also be due to progressive obesity, lack of exercise, intercurrent illness, and treatment nonadherence. A variety of therapeutic options are available for patients not achieving glycemic goals.

Notably, this patient was on appropriate first-line therapy for his T2DM, but now his HbA1c is above target. He has been counseled about lifestyle modification, which should be reinforced, but he is likely to need additional antihyperglycemic agent(s), given the magnitude of elevation of his HbA1c. Considerations for the choice of the second (and third) agents are based on efficacy, side-effect profiles, risk of hypoglycemia, changes in weight, and cost (Table 2). In patients with established heart disease, it is prudent to avoid hypoglycemia. Important comorbidities that will alter the selection of diabetes therapy include heart failure, chronic kidney disease, and liver dysfunction. There are no appreciable pharmacological interactions between diabetes therapies and major drug classes indicated for cardiovascular disease, although β-blockers may attenuate patient recognition of hypoglycemia. A stepwise approach is presented in the Figure.

**Incretin-Based Therapies for Diabetes Mellitus**

Incretin-based therapies are newer approaches available to treat hyperglycemia. Incretins are hormones produced in the small intestine that enhance glucose-stimulated insulin secretion and inhibit glucose-stimulated glucagon suppression. Dipeptidyl peptidase-4 (DPP-4) inhibitors are administered orally and are intermediate among approved oral antihyperglycemic agents in glycemic-lowering potency, have low risk for hypoglycemia, are weight neutral, and are well tolerated. In comparison, glucagon-like peptide-1 (GLP-1) receptor agonists are administered through subcutaneous injections, are highly effective for glucose lowering without hypoglycemia, and induce satiety and weight loss. Gastrointestinal side effects (nausea, vomiting) limit their use in some patients.

A meta-analysis of randomized, controlled trials suggests possible protection from cardiovascular events with the use of DPP-4 inhibitors and neutral to protective effects with GLP-1 receptor agonists. However, 2 large, placebo-controlled, randomized,
Table 2. Major Pharmacotherapeutic Options for T2DM*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Biguanide</th>
<th>Sulfonylurea†</th>
<th>Thiazolidinedione</th>
<th>α-Glucosidase Inhibitor</th>
<th>DPP-4 Inhibitor</th>
<th>GLP-1 Receptor Agonist</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked in US</td>
<td>Metformin (Glucophage, Glucophage XR, Fortamet, Glumetza, Riomet)</td>
<td>Glipizide (Glucotrol, Glucotrol XL), glyburide (Amaryl), glimepiride (Amaryl), glyburide (Diabeta, Micronase, Glynase PresTab)</td>
<td>Rosiglitazone† (Avandia), pioglitazone (Actos)</td>
<td>Acarbose (Precose)</td>
<td>Sitagliptin (Januvia), linagliptin (Tradjenta), saxagliptin (Onglyza)</td>
<td>Exenatide (Byetta, Bydureon), lixisenatide (Victoza)</td>
<td>Various short- to long-acting preparations available</td>
</tr>
</tbody>
</table>

Glycemic effects

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>High</th>
<th>High</th>
<th>High</th>
<th>Moderate</th>
<th>Moderate</th>
<th>High</th>
<th>Highest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemic risk</td>
<td>Low§</td>
<td>Moderate</td>
<td>Low§</td>
<td>Low§</td>
<td>Low§</td>
<td>Low§</td>
<td>High</td>
</tr>
</tbody>
</table>

Nonglycemic effects

<table>
<thead>
<tr>
<th>Weight</th>
<th>Neutral/loss</th>
<th>Gain</th>
<th>May reduce ischemic preconditioning</th>
<th>Neutral (products may have differential effects)</th>
<th>May lower MACEs</th>
<th>Neutral</th>
<th>Loss</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>May lower MACEs</td>
<td>Edema, exacerbation of heart failure, long-bone fractures</td>
<td>Flatulence, diarrhea</td>
<td>Pancreatitis (rare)</td>
<td>Gastrointestinal, pancreatitis (rare)</td>
<td>Hypoglycemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Major side effects(s)

| Gastrointestinal, lactic acidosis (rare) | Hypoglycemia | Edema, exacerbation of heart failure, long-bone fractures | Flatulence, diarrhea | Pancreatitis (rare) | Gastrointestinal, pancreatitis (rare) | Hypoglycemia |

Avoid use in

| Impaired renal function | Hypoglycemia prone | Heart failure, personal/family history of bladder cancer | None | Prior pancreatitis | Prior pancreatitis | Hypoglycemia prone |

| Cost | Low | Low | High | High | High | High | Variable |

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular event; and T2DM, type 2 diabetes mellitus.

*Represents major categories of drugs for the treatment of type 2 diabetes mellitus (does not include bile acid sequestrants, dopamine receptor agonists, amylinomimetics, and sodium-glucose cotransporter 2 inhibitors).

†Current second-generation sulfonylureas (meglitinides share similar features).

§Hypoglycemia does not occur when used as monotherapy.

‖Because of the potential cardiovascular concerns with rosiglitazone, it is currently available only through a restricted distribution program.

°Saxagliptin has been associated with increased hospitalizations for heart failure. This has not been reported with other DPP-4 inhibitors.

clinical trials to assess cardiovascular outcomes using different DPP-4 inhibitors, saxagliptin15 and alogliptin,16 have demonstrated noninferiority for cardiovascular outcomes. Results of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus (SAVOR-TIMI-53) trial15 suggest noninferiority of saxagliptin in patients with T2DM with either a history of established cardiovascular disease or multiple risk factors for the composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke when added to a patient’s current standard of care (with or without other diabetes therapies) compared with placebo. However, an increase in hospitalizations for heart failure15 in those taking saxagliptin was observed. While concerns about potential increased risk for pancreatitis have been raised, these 2 randomized trials do not show increased pancreatitis risk with DPP-4 inhibition.15,16 Although DPP-4 inhibitors are patent protected and more costly, these trials demonstrating neutral cardiovascular effects will likely move these agents toward preferred second-line therapies.

GLP-1 receptor agonists may move toward first-line agents if ongoing cardiovascular outcome trials demonstrate clear benefits. They are among the more effective agents available for glycemic lowering, do not cause hypoglycemia in the absence of insulin-provisional therapies, are associated with modest weight loss, and have favorable effects on cardiovascular risk factors. When administered by injection, once-weekly dosing for exenatide (Bydureon) may improve compliance and patient satisfaction. The GLP-1 receptor is expressed in cardiac myocytes, endothelial cells, macrophages, and regions of the central and peripheral nervous system that regulate cardiovascular function. Thus, GLP-1 receptor activation has direct and indirect actions on the heart and vasculature.17 GLP-1 receptor activation is directly cardioprotective in animals and may be in humans. Notably, GLP-1(9–36), a metabolite of endogenous GLP-1, also has cardioprotective properties, complicating extrapolation of cardiovascular actions attributable to DPP-4 inhibitors and structurally distinct GLP-1 receptor agonists.17 GLP-1 receptor activation reduces postprandial intestinal lipoprotein secretion in rodents and humans and attenuates the development of atherosclerosis in mouse models of dyslipidemia. Activation of GLP-1 receptors on monocytes and macrophages reduces inflammation. Nevertheless,
it is prudent to remain cautious when extrapolating findings from surrogate end points.

**Second- and Third-Line Therapies for T2DM Management**

Sulfonylureas have been the mainstay of oral antihyperglycemic agents since the 1950s. They are initially highly effective but have a high secondary failure rate. Hypoglycemia is less common in patients with an initially high HbA1c. Cardiovascular benefits emerge over time in patients who have been treated with sulfonylureas.6 The sulfonylurea gliclazide, available in Europe, when used with other drugs as required, reduced microvascular events but had no effect on major cardiovascular events in the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial. However, there is concern that sulfonylureas may reduce ischemic preconditioning, an effect seen predominantly with first-generation sulfonylureas.18 Meglitinides, another class of oral antihyperglycemic agents, are also insulin secretagogues, bind to the same receptor on the pancreatic β cell, and share many features with sulfonylureas, although they have different pharmacokinetic features.

Insulin is appropriate as a second- or third-line therapeutic agent. It has the highest efficacy but highest risk of hypoglycemia. Indeed, in the presence of marked hyperglycemia, significant weight loss or other symptoms of hyperglycemia, severe concurrent illness, or anticipated surgery, insulin would be the most appropriate second-line therapy. However, insulin can be administered safely even in patients with early diabetes mellitus.11 Insulin dosing can be adjusted frequently to achieve glycemic targets, with immediate reductions for the occurrence of hypoglycemia. Insulin administration is associated with increased risk of hypoglycemia and weight gain. Hence, in the absence of severe symptoms, other antihyperglycemic agents are often favored before insulin is considered. Beyond 3-drug combinations, one should strongly consider switching to insulin-based therapies, especially for patients already on polypharmacy regimens, which can prove challenging for adherence. Basal insulin with once-daily long-acting insulin is initially preferred because it can minimize hypoglycemia and may be used in combination with most other

Insulin is appropriate as a second- or third-line therapeutic agent. It has the highest efficacy but highest risk of hypoglycemia. Indeed, in the presence of marked hyperglycemia, significant weight loss or other symptoms of hyperglycemia, severe concurrent illness, or anticipated surgery, insulin would be the most appropriate second-line therapy. However, insulin can be administered safely even in patients with early diabetes mellitus.11 Insulin dosing can be adjusted frequently to achieve glycemic targets, with immediate reductions for the occurrence of hypoglycemia. Insulin administration is associated with increased risk of hypoglycemia and weight gain. Hence, in the absence of severe symptoms, other antihyperglycemic agents are often favored before insulin is considered. Beyond 3-drug combinations, one should strongly consider switching to insulin-based therapies, especially for patients already on polypharmacy regimens, which can prove challenging for adherence. Basal insulin with once-daily long-acting insulin is initially preferred because it can minimize hypoglycemia and may be used in combination with most other
therapies. If multiple daily injections become necessary, oral antihyperglycemic regimens should be reassessed and simplified. Some patients who require multiple daily insulin injections may find insulin delivery easier with a subcutaneous insulin infusion pump. However, benefits of a pump compared with multiple daily injections have not been as firmly established in patients with T2DM, in contrast to patients with type 1 diabetes mellitus.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial showed equivalent cardiovascular outcomes with initial insulin-provisional or insulin-sparing therapeutic approaches. Although one cannot draw conclusions on specific drug safety on the basis of this trial, BARI-2D provides support that either approach is clinically sound in patients with diabetes mellitus and established coronary artery disease.

Other medications to improve glycemica are also available, including α-glucosidase inhibitors, bile acid sequestrants, amylinomimetics, and dopamine agonists. They are, however, less potent glycemic-lowering agents and would be unlikely to get this patient to goal.

Finally, the US Food and Drug Administration granted the first approval for a sodium-glucose cotransporter 2 inhibitor, canagliflozin, in March 2013. Sodium-glucose cotransporter 2 inhibitors block glucose reabsorption from the kidney, thereby promoting glycosuria, and have modest weight loss effects. However, there is little information on long-term glycemic durability and cardiovascular safety for this newest family of antihyperglycemic agents. Preliminary results from the Canagliflozin Cardiovascular Assessment Study (CANVAS) showed that although canagliflozin was neutral for major adverse cardiac events overall, there was an increased signal in stroke incidence in the first 30 days of treatment. The small numbers affected make it difficult to be certain of this risk.

Returning to the patient, his glycemic control should be re-evaluated at ≥3-month intervals, and the therapeutic approach should be advanced in the event that glycemic goals are not achieved. Importantly, providers must attend to the coexistence of multiple cardiovascular risk factors in the patient with T2DM and adopt a multidisciplinary strategy to manage dyslipidemia, hypertension, and the prothrombotic state commonly associated with diabetes mellitus.

Sources of Funding

This work was supported by a NIH Diabetes Endocrinology Research Center (DERC) grant to Joslin Diabetes Center (NIH P30-DK-0368-36).

Disclosures

Dr Goldfine receives research funding from the National Institutes of Health and the American Diabetes Association, investigator-initiated research support from Daiichi Sankyo, and research materials for investigator-initiated work from Caraco Pharmaceuticals, Amneal Pharmaceuticals; Lifescan, a Division of Johnson & Johnson; Novo Nordisk; Merckodia; and Nestle. Dr Phua received fellowship funding from Alexandra Health Pte Ltd (Singapore). Dr Abrahamson received consulting fees from Novo Nordisk, Halozyme, and Boehringer Ingelheim.

References


Glycemic Management in Patients With Coronary Artery Disease and Prediabetes or Type 2 Diabetes Mellitus
Allison B. Goldfine, Eng-Joo Phua and Martin J. Abrahamson

Circulation. 2014;129:2567-2573
doi: 10.1161/CIRCULATIONAHA.113.006634
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/129/24/2567

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/