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Rare Incidence of Congestive Heart Failure in Gastrointestinal Stromal Tumor and Other Sarcoma Patients Receiving Imatinib Mesylate (IM)

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Abstract

Background—We sought to determine the incidence and severity of cardiovascular toxicity due to imatinib mesylate(IM) in GIST and other sarcoma patients, and to explore cardiotoxicity due to IM using cell culture and in vitro models.

Methods—To determine the incidence and significance of serious cardiac adverse events in GIST and other sarcoma patients receiving IM, we performed a retrospective analysis of 219 consecutive patients treated with IM. In vitro studies of IM on cultured cardiomyocytes and biochemical studies of cardiac lysates from mice treated with IM were performed to define the potential cardiotoxic effects of IM.

Results—Grade III or IV potentially cardiotoxic adverse events (mostly edema or effusions) occurred in 8.2% of patients, were manageable with medical therapy, and infrequently required dose reduction or discontinuation of IM. Arrhythmias, acute coronary syndromes, or heart failure were uncommon, occurring in less than 1% of treated patients. However, administration of imatinib in a mouse model system resulted in inhibition of activation of protein kinases that are known to be important in the cardiac stress response.

Conclusion—We conclude that imatinib is an uncommon cause of cardiotoxicity and that the cardiovascular adverse events that occur are manageable when recognized and treated. Nevertheless, our pre-clinical findings suggest that imatinib remains a potential cardiotoxin. Furthermore the cardiac consequences of long-term imatinib therapy remain unknown. We

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therefore recommend treatment of risk factors for cardiovascular disease in imatinib treated patients in accord with the American Heart Association guidelines for the prevention and treatment of heart failure.

Keywords

Imatinib; congestive heart failure; cardiotoxicity; sarcoma; GIST

Introduction

The use of IM as a therapy targeting an essential signaling pathway (Abl kinase) in patients with chronic myelogenous leukemia (CML) represents a new paradigm in rational drug design, and has shown remarkable efficacy in the treatment of patients with early-chronic phase and advanced stage CML[1, 2]. Similarly, IM has been shown to be extremely effective in patients with advanced gastrointestinal stromal tumor (GIST) through inhibition of the kinase KIT [3]. The promise of molecularly targeted cancer therapy is based upon the premise that by specifically inhibiting molecules associated with tumor growth, such therapies will be highly effective in treating cancer without adversely affecting normal organs.

Although targeted cancer therapies are typically aimed at molecules that are aberrant in cancer cells, the fact remains that many receptor tyrosine kinases are expressed in normal tissues, and these molecules may play a role in the normal physiology of many organ systems, including the cardiovascular system. An example of this was seen in the treatment of breast cancer patients with the monoclonal antibody trastuzumab, whose target is the receptor tyrosine kinase ErbB2, the product of the *Her2/Neu* gene. 7% of patients treated with trastuzumab after anthracycline exposure developed cardiomyopathy, and 29% of the patients treated concurrently with trastuzumab and anthracycline developed cardiomyopathy[4]. Subsequent pre-clinical studies demonstrated the essential role of ErbB2 signaling in normal cardiac development and in the cardiac response to stress[5–7].

Recent work has demonstrated that IM can cause significant cardiac dysfunction when administered to mice at clinically relevant dosages[8, 9]. Imatinib treated mice developed depressed cardiac function, abnormalities in the ER stress response within the heart, and mitochondrial abnormalities. Similar mitochondrial abnormalities were also seen in cardiac tissue obtained from patients treated with imatinib who also developed cardiac dysfunction and heart failure (HF).

This study led to widespread concern about the potential cardiotoxicity of IM and prompted a revision of the drug label to include careful monitoring of patients with cardiac disease or risk factors for heart failure. Subsequently, multiple studies reported a low incidence of clinically important HF in patients with both CML[10] and GIST[11, 12] treated with imatinib.

To further explore the effects of imatinib on cardiac function of GIST patients, we performed a retrospective analysis of our clinical trial database for analysis of potential cardiac adverse events. We found that adverse cardiac events in GIST patients treated with IM were uncommon and manageable and rarely required discontinuation of IM therapy. Consistent with these clinical findings, we found that in contrast to doxorubicin, imatinib did

not cause apoptosis in cardiac myocytes in vitro. However, while in vivo administration of imatinib to mice did not cause overt cardiac failure, it did result in inhibition of the protein kinases Akt and Erk 1/2, both of which have been shown to play a cardioprotective role in the setting of vascular stress[13].

METHODS

Clinical Studies

We reviewed all sarcoma patients enrolled in clinical trials with IM from 27 December 2000 to 11 May 2006 with institutional review board approval. From these databases, 219 consecutively treated patients were evaluated for the occurrence of Grade III or IV potential cardiac adverse events (PCAEs), including shortness of breath, dyspnea on exertion, chest pain, edema, pleural effusion, ascites, cardiac ischemia, and arrhythmia. The baseline characteristics of these patients are shown below in Table 1.

In patients with PCAEs, the clinical histories were reviewed in detail. Chest x-rays, echocardiograms, electrocardiograms, and relevant laboratory studies were reviewed for each patient to determine the possibility of cardiac toxicity. Signs and symptoms of HF that were specifically searched for in the chart review include orthopnea, paroxysmal nocturnal dyspnea, and jugular venous distention. Radiographic criteria used to diagnose HF include pulmonary vascular congestion and cardiac silhouette enlargement. Echocardiograms of all patients with PCAE were examined in detail by a single cardiologist (J.C.P.) who was unaware of any clinical information.

Cardiomyocyte culture

HL-1 cardiomyocytes were used for in-vitro studies and were grown in Claycomb media (SAFC Biosciences, Lenexa, KA) as previously described[14], including 100 uM norepinephrine (Sigma-Aldrich, St. Louis, MO) and 10 % fetal bovine serum (SAFC Biosciences).

In vitro apoptosis assay

Hl-1 cardiomyocytes were serum starved and treated with imatinib mesylate (Novartis) or vehicle control overnight. Cells pre-treated with imatinib or control were exposed to doxorubicin (Sigma-Aldrich) for two hours in serum-free media. Lysates from drug-exposed cells were harvested and caspase activity was measured as an index of cardiomyocyte apoptosis as previously described[15]. Caspase activity was measured using the Caspase-Glo 3/7 Assay System (Promega, Madison, WI).

In vivo imatinib administration

Imatinib mesylate was administered to mice at 50 mg/kg daily for a period of up to six weeks. All animal work was done according to animal protocols approved by the institutional animal care and use committee. Imatinib was dissolved in saline and administered by gavage. Control mice were administered identical amounts of vehicle control by gavage. 48 hours after the final dosage of imatinib, mice were sacrificed, and

hearts and lungs were immediately harvested for weighing. Hearts were then flash frozen in liquid nitrogen until ready to be used for biochemical analysis.

Western blotting

Protein lysates isolated from murine left ventricles were isolated using cell lysis buffer (Cell Signaling Technology, Danvers, MA) with phosphatase inhibitors. Lysates were separated by gel electrophoresis and blotted using the Novex system (Invitrogen, Carlsbad, CA). Blots were probed with antibodies directed against phospho Akt (Ser473), phospho Erk 1/2 (Thr202/Tyr204), total Akt, total Erk 1/2 (Cell Signaling Technology). Probing with an anti-GAPDH antibody (Sigma-Aldrich) was also performed to control for equal protein loading.

RESULTS

Of the 219 patients evaluated, 18 (8.2%) were identified as having a Grade III or IV PCAE. The specific characteristics, along with lists of the established risk factors for coronary artery disease (CAD) of these 18 patients, are shown in Table 2. Notably, the median age of patients with Grade III or IV PCAE was 65 (range 21–88). In total, 13 (72%) had metastatic disease and 10 (56%) had a history of hypertension. The median IM dose in patients with PCAE was 600 (range 400–800) mg daily. The median number of days the patient was on IM prior to PCAE was 174 (range 17–1588). None of these features were significantly different from those seen in the overall patient population.

Of the 219 patients that we studied, 7 (3.2%) manifested Grade 3 or 4 dependent edema or effusion, 5 (2.3%) had objective evidence of cardiac ischemia or chest pain, 2 (0.9%) had documented arrhythmias, 2 (0.9%) had Grade 3 or 4 dyspnea, 1 (0.4%) had objective left ventricular (LV) dysfunction by echocardiography, and 1 (0.4%) went into cardiac arrest.

Of the 7 patients (3.2%) who manifested edema or effusion, 2 (0.9%) had a pleural effusion, 4 (1.8%) had ascites, all 7 had lower extremity edema, and none had objective LV dysfunction or any signs, symptoms, or radiographic evidence of HF. Of the 4 patients (1.8%) that had echocardiograms after development of the PCAE, all had normal cardiac ejection fractions (EF > 55%). Interventions in these 7 patients included diuretics for 6 (2.8%), ACE-inhibitors and beta-blockers for 2 (0.9%), thoracentesis and paracentesis for 5 (2.3%), a continued, unchanged IM dose for 3 (1.4%), a continued, reduced IM dose for 3 (1.4%), and discontinuation of IM for 1 patient (0.5%). This final patient had their IM dose discontinued due to the combination of Grade III/IV edema and progression of disease while on 800 mg IM daily.

Of the 5 patients (2.3%) who had chest pain or possible cardiac ischemia, electrocardiograms revealed that 1 (0.5%) had new Q-waves or ST-segment elevation and 1 (0.5%) had new ST-segment depression or T-wave inversion. 2 patients (0.9%) had elevated cardiac injury biomarkers. 1 patient (0.5%) had a positive stress test. 3 patients (1.4%) required cardiac catheterization. 2 patients (0.9%) had developed flow-limiting CAD. An ST-segment elevation and Q-wave myocardial infarction occurred in one patient in the post-operative period after neoadjuvant therapy with IM for GIST. This patient was diabetic, and had a history of hyperlipidemia. Another patient with multiple risk factors for CAD had a

positive stress test 10 days after starting neoadjuvant IM as part of a pre-operative evaluation. The patient had no symptoms. The patient was found to have severe flow-limiting CAD and had multiple coronary stents placed. All 5 patients (2.3%) above continued on IM without dose reduction.

We were able to identify only one patient (0.5%) who clearly developed heart failure associated with severe morbidity and mortality while on IM. The patient was a 61-year-old woman who was started on 400 mg IM daily for metastatic GIST. The patient's prior history included two-vessel coronary artery bypass surgery but no history of heart failure or left ventricular dysfunction. After two years of IM therapy, the patient underwent surgical resection of the metastatic GIST. Pre-operative evaluation revealed normal LV function and only mild anterior wall ischemia on stress testing. Post-operatively there was steady progression of the disease over a two-year time period, which resulted in the subsequent increase in the IM dose to 800 mg daily. After further disease progression on IM, perifosine, an antiproliferative and proapoptotic agent under investigation, was added to the patient's treatment regimen. In hundreds of patients treated with perifosine there has been no association with a decrease in cardiac function alone or in combination with kinase inhibitors. One month later, the patient presented with orthopnea, severe fatigue, and dyspnea. Echocardiography at the time of presentation with symptoms of congestive heart failure confirmed profound decrease in LV function (EF < 20%) compared to the pre-operative echocardiography performed two years earlier (Fig. 1). Electrocardiogram revealed no evidence of new ischemic changes, Troponin I levels were <0.1 and BNP = 2399 pg/mL (normal < 50 pg/mL). After further progression of both GIST and CHF, the patient was treated with a regimen of diuretics, ACE-inhibitors, and beta-blockers with concurrent discontinuation of IM and perifosine therapy. The patient expired several months later from progression of disease.

Our clinical data suggests that clinically apparent, IM-associated cardiac abnormalities are uncommon in GIST patients. However, this clinical observation does not exclude sub-clinical or delayed cardiovascular effects of imatinib. In order to further explore the cardiotoxic effects of imatinib, we used the HL-1 cardiomyocyte cell line as a model system. HL-1 cells are beating cardiomyocytes derived from a primary atrial tumor whose use as a model system for in vitro studies has been well-validated[14]. As has been described previously[16], we observed a dose-dependent increase in apoptosis, assayed by caspase 3/9 activation, in cardiomyocytes treated with doxorubicin (Figure 2A). In contrast, treatment with IM over a broad concentration range had no effect on cardiomyocyte apoptosis in vitro (Figure 2B). Furthermore, we did not observe enhancement of doxorubicin-mediated apoptosis by imatinib over a broad dose range (Figure 2C). These findings importantly contrast the cardiotoxicity of imatinib to the well-established pro-apoptotic effects of anthracycline-based chemotherapy [17].

To study the functional and biochemical effects of IM in the heart in the in vivo setting, we treated mice with IM in at 50 mg/kg/d for a period of 4 weeks; a dosage regimen similar to those used previously in vivo cancer efficacy studies[18–20]. In imatinib treated mice, we saw no evidence of overt cardiac dysfunction as measured by heart weight to body weight ratios (Fig. 3A) or lung weight to body weight ratios (not shown), an index of pulmonary edema.

To further explore the effects of imatinib on the heart, we analyzed cardiac lysates from hearts of imatinib treated mice for activation of established downstream targets of tyrosine kinases that are known to be cardioprotective under conditions of stress. Strikingly, we saw a marked reduction in levels of phosphorylated Akt (Figure 3B) in cardiac tissue from imatinib treated mice compared with controls. Multiple studies from a variety of mouse models implicate Akt as a central regulator of maintenance of cardiac eutrophy and as a regulator of the cardiac response to physiologic stress[21]. In addition, we found a marked reduction in phosphorylation of the Erk 1/2 branch of the MAPK signaling pathway in imatinib treated hearts compared with controls (Figure 3C), obtaining a significant, 50% decrease in the ratio of phospho- to total Erk 1/2 (Figure 3D). Like Akt, Erk 1/2 activation has been shown to be critical for maintenance of cardiac function under conditions of stress[22]. Notably, imatinib did not alter phosphorylation of the p38 branch of the MAPK signaling cascade (data not shown), whose role in cardiac protection is less well-established[23]. These findings suggest that while imatinib does not cause overt cardiac failure, it does affect signaling cascades that may predispose to the development of cardiac failure under conditions of physiologic stress.

DISCUSSION

In patients with GIST treated with IM, cardiac dysfunction does not appear to be causally related to development of severe edema or effusion in most cases. Overt CHF with new LV dysfunction during IM treatment in GIST patients occurred in 1/219 patients (0.4%), and the causal relationship of imatinib or perifosine to the development of CHF in that case is not clear. GIST patients with pre-existing heart disease or multiple risk factors for CAD were more likely to experience cardiac adverse events while being treated with IM than those with no history of cardiac disease. Since this study does not include a placebo arm for comparison, it is not possible to know whether this is any higher than the population of patients not treated with imatinib. PCAEs due to IM in GIST patients are uncommon, manageable, and rarely require IM or other therapy to be discontinued or dose-reduced.

Furthermore, we used an in vitro assay to show that the effects of imatinib on cardiomyocytes are distinct from the established pro-apoptotic effects of doxorubicin. However, while administration of imatinib at clinically relevant dosages did not alter mouse cardiac function in vivo, we found that pathways that are known to be critical to the cardiac stress response are strongly inhibited after several weeks of imatinib therapy. Such findings suggest that imatinib treatment may increase the likelihood of development of cardiac dysfunction under conditions of stress. Alternatively, it is possible that compensatory mechanisms independent of activation of Akt and ERK1/2 may minimize cardiac toxicity due to imatinib under conditions of stress. Studies designed to understand the effects of imatinib on the cardiac response to vascular stress are part of the ongoing work in our laboratory.

The effects on cardiac Akt and ERK1/2 phosphorylation due to imatinib are distinct but are possibly additive to the effects of imatinib on the cardiac ER stress response that have been previously reported[8]. The upstream targets of imatinib that result in blockade of activation Akt and ERK1/2 are of great interest to us. Several reports suggest that Abl kinase is a

critical target of imatinib in the cardiomyocyte[8, 9]. Although the MAPK and Akt pathways are putative effectors of Abl kinase signaling, a direct effect on this signaling pathway in cardiac myocytes due to imatinib has not previously been described.

Another possibility is that imatinib exerts its effects on the heart via inhibition of PDGFR signaling. PDGFR is an established target of imatinib[24], and both the Akt and MAPK pathways are key effectors of PDGFR signaling[25]. Although the role of PDGFR signaling in the heart is largely unexplored, recent work suggests that activation of PDGFR in the cardiomyocyte may exert a cardioprotective role through effects on Akt signaling[26] The relative contributions of inhibition of Abl, PDGFR or other targets to the effects of imatinib on the MAPK and Akt pathways in cardiomyocytes are the subject of intense study in our laboratory.

Our pre-clinical findings highlight several important points about the clinical cardiovascular effects of imatinib that are worthy of mention. First of all, previous reports and our clinical findings suggest that patients with underlying cardiovascular disease may be at greater risk for developing the cardiovascular abnormalities associated with imatinib therapy[8, 10]. It should be noted that there is as yet no conclusive evidence that these adverse events are indicative of drug toxicity. One weakness of our study is that it did not include careful evaluation of a control group with similar cardiac histories but without GIST or imatinib treatment. Another weakness of our study and of other studies that have determined the incidence of PCAEs putatively due to imatinib and other tyrosine kinase inhibitors is that these studies have been retrospective in nature, and have not relied on careful, prospectively defined measurements of cardiac function. The clinical diagnosis of heart failure in cancer patients can be enormously challenging to make without the use of prospective, well-defined endpoints, due to the overlap of the cardinal symptoms of heart failure- dyspnea, fatigue, and edema- that are very common in cancer patients, including GIST patients treated with imatinib. Thus, the reported incidence of heart failure due to imatinib therapy, particularly when mild and subclinical, may be underestimated by our study and others. Furthermore, little is known about the effects of long-term administration of imatinib and other tyrosine kinase inhibitors on cardiac function. Prospective studies with cardiac monitoring will be required to answer these questions, and based upon our pre-clinical findings, we believe that such studies are warranted.

While we await such studies, we believe that the wealth of evidence suggests that cardiac complications in patients treated with imatinib are manageable and should not be a reason to withhold imatinib therapy from cancer patients who would derive benefit. At the same time, in light of the current mechanistic studies and clinical observations, a practical approach to preventing potential cardiac complications of imatinib is needed. One such approach that seems to be applicable to patients treated with imatinib is based upon the recently published guidelines from the American Heart Association for the management of congestive heart failure (Figure 4). In this classification scheme, a new area of focus is the so-called Stage A patient, a patient without clinical evidence of cardiac dysfunction but at risk for heart failure. Management of such patients involves modification of risk factors that may predispose the patient to heart failure, including treatment of blood pressure and hypercholesterolemia and encouragement of smoking cessation (see Figure 4).

Recently, the Food and Drug Administration (FDA) has approved the adjuvant use of imatinib for patients who have had their GIST resected without specifying the duration of therapy. Although these patients may be cured of their GIST, they may be taking imatinib for many years. Early detection and management of HF of any etiology is important in this patient population. Therefore, based upon its potential cardiotoxicity, chronic administration, and long-term patient survival, we believe that patients treated with imatinib can be thought of as Stage A patients (at risk for heart failure) and that application of the AHA guidelines for the Stage A patient is a reasonable approach to prevent long-term cardiac complications that occur in patients treated with this remarkable drug.

Acknowledgments

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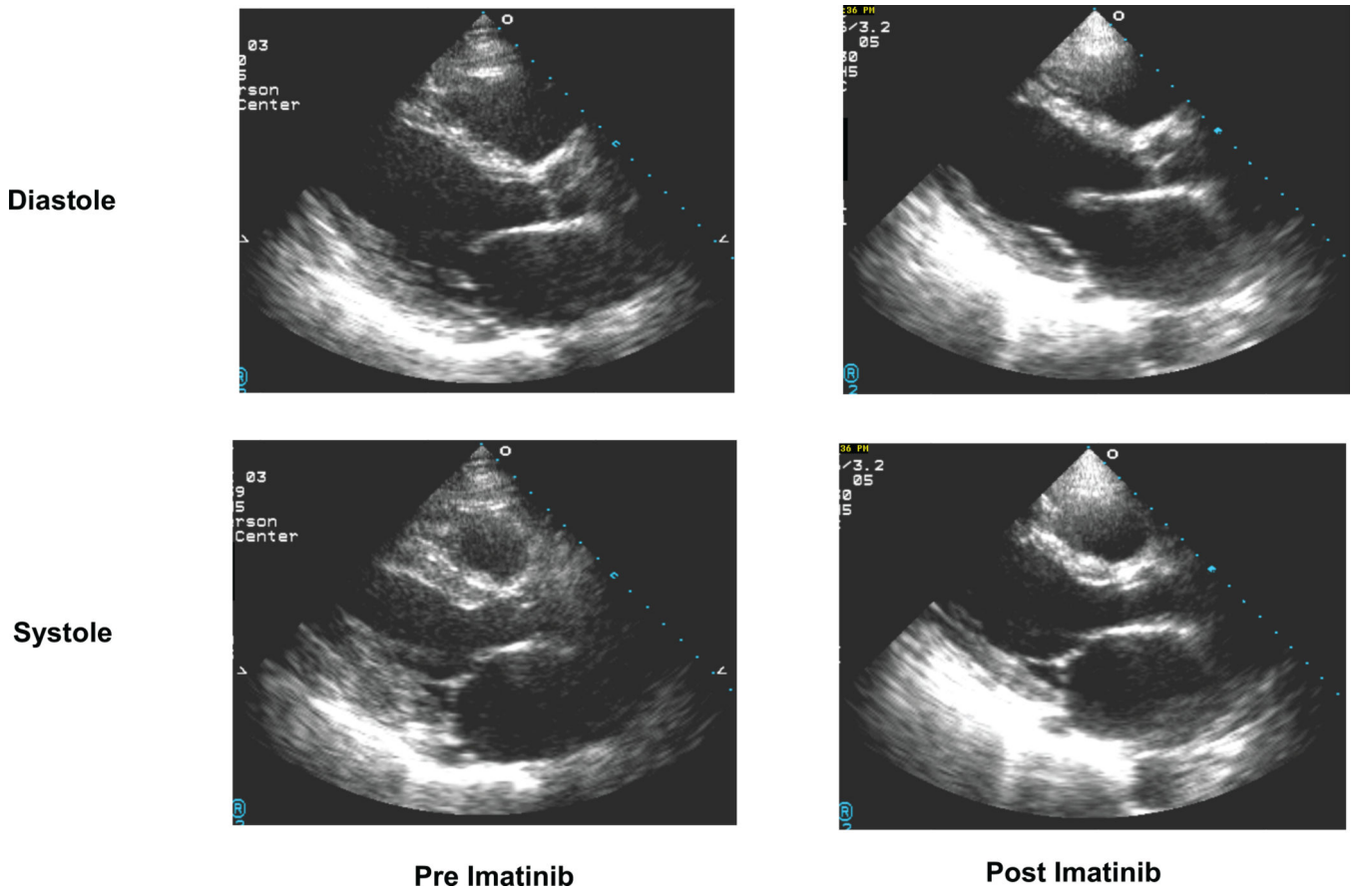

Figure One. New left ventricular dysfunction in a patient treated with imatinib mesylate

Long axis echocardiographic images shown at end diastole (top panels) and end systole (bottom panels) demonstrate profound changes in cardiac function in a patient who developed heart failure while undergoing therapy with imatinib. In contrast to the normal systolic myocardial contraction seen in June, 2003 (left hand panels, “Pre Imatinib”), prior to imatinib therapy, cardiac systolic function was markedly reduced at the time of presentation with heart failure in December, 2005 (right hand panels, “Post Imatinib”), at which time the calculated left ventricular ejection fraction was 20–25%.

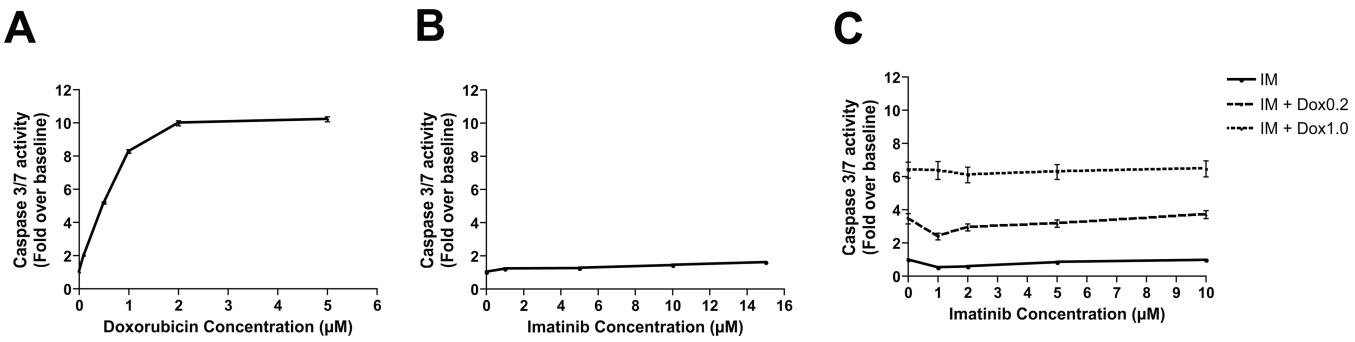

Figure Two. Imatinib mesylate does not contribute to cardiomyocyte apoptosis alone or in combination with doxorubicin

HL-1 cardiac myocytes were treated with doxorubicin (A), imatinib mesylate (B), or both drugs (C) overnight at the indicated concentrations. The following day, cell lysates were harvested and assayed for caspase 3/7 activity, a marker of cellular apoptosis. While doxorubicin showed a prominent, dose-dependent increase in caspase 3/7 activity (A), imatinib mesylate alone had minimal effect on caspase activity (B), and increasing concentrations of imatinib did not substantially increase caspase activity in cells treated with doxorubicin at 0.2 or 1.0 uM (C). Results shown are mean values of triplicate independent treatments, and are representative of two independent experiments.

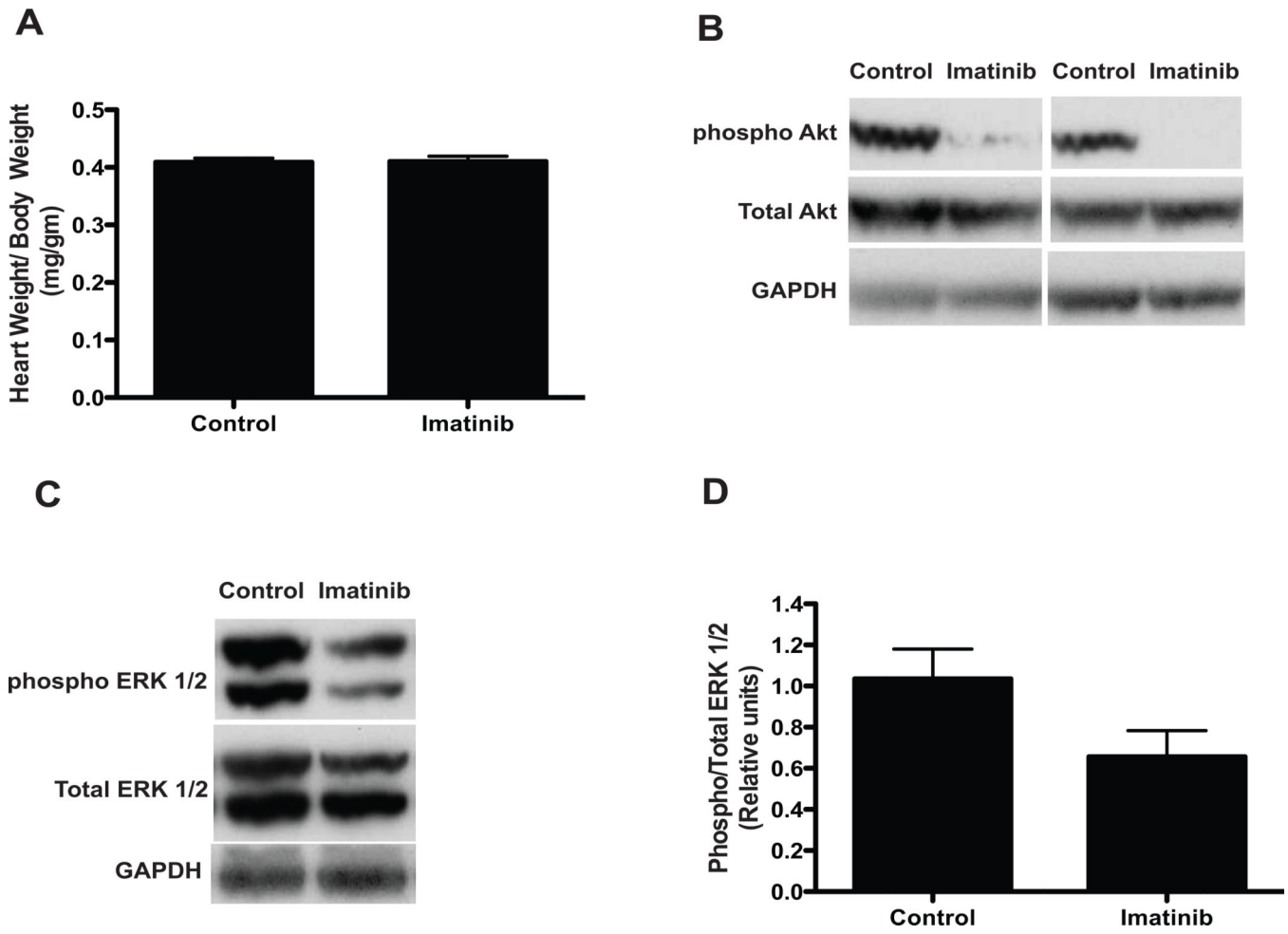

Figure Three. Imatinib mesylate treatment blocks activation of the kinases Akt and Erk 1/2 in the heart

Mice were treated with imatinib mesylate at a dosage of 50 mg/kg/day for a total of 4 weeks. (A) Heart weight/body weight ratios were unchanged in imatinib treated mice. (B) Phosphorylation of the protein kinase Akt was markedly reduced in the hearts of imatinib treated mice compared with control mice, while total Akt levels were unchanged. Results are representative of data from 5 pairs of mice. (C) Phosphorylation of the protein kinase Erk 1/2 was also significantly reduced in hearts from imatinib treated mice compared with controls. (D) Quantitative densitometry reveals a 40% decrease in phospho/total Erk 1/2 levels from hearts of imatinib treated mice compared with controls (n=5 in each group, $p < 0.005$).

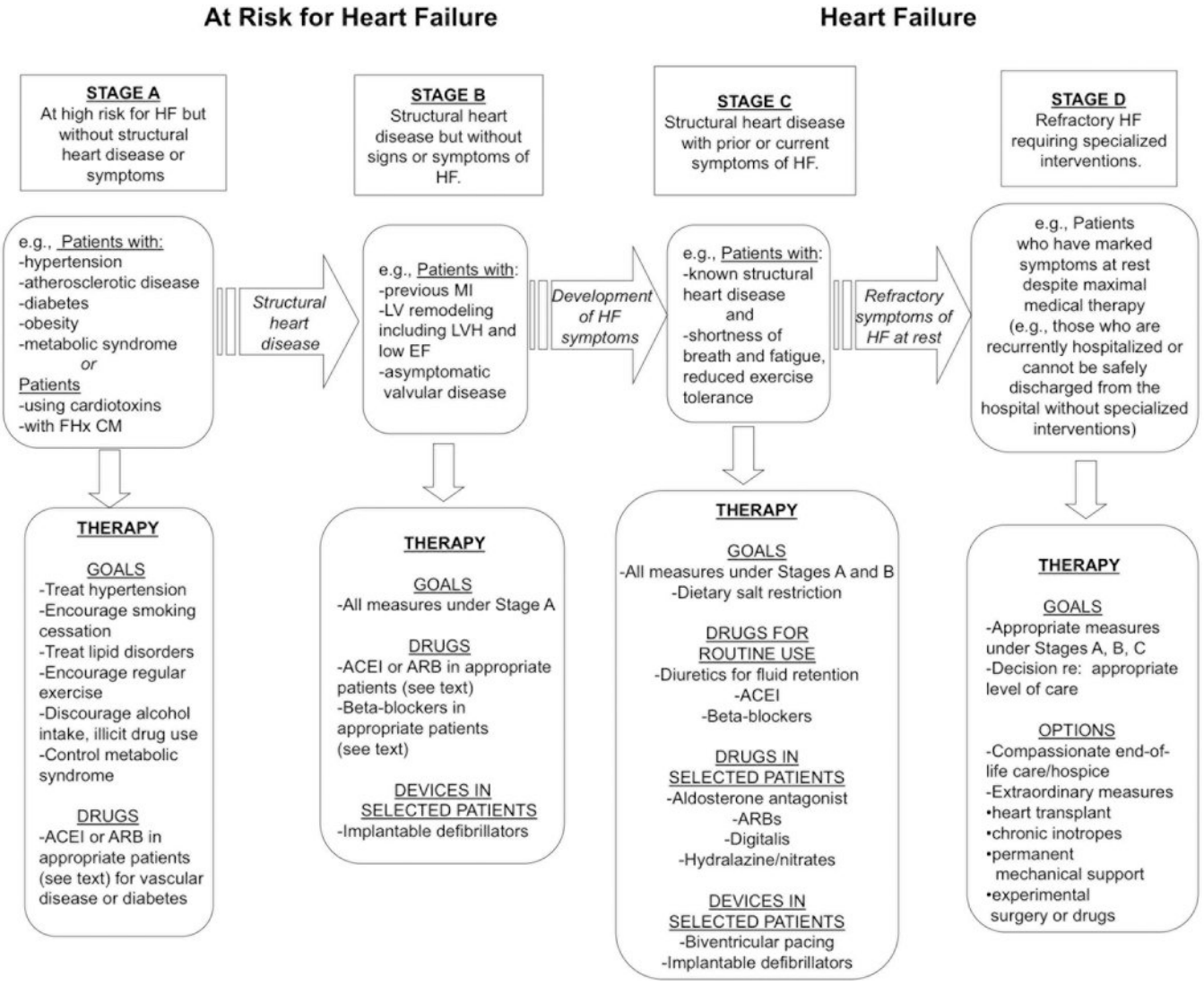

Figure Four. AHA Guidelines for the Classification and Treatment of Congestive Heart Failure

Stages in the development of heart failure/recommended therapy by stage. GIST patients treated with imatinib may be at risk for the development of heart failure, and thus, may be treated according to the treatment recommendations for Stage A patients. Reprinted with permission from the American Heart Association. HF = heart failure; FHx CM = family history of cardiomyopathy; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; MI = myocardial infarction; LVH = left ventricular hypertrophy; EF = ejection fraction

Table 1

Demographic and baseline clinical characteristics of patients (n=219)

Characteristic	Value (range)
Median Age	58 (16 – 92)
Gender	
Male	116
Female	103
Race	
Caucasian	169
African-American	22
Hispanic	19
Asian	7
American Indian	1
Other	1
Median IM Dose	600 (400 – 800) mg daily

Table 2

Characteristics of IM Treated Patients with PCAEs

Patient #	Age	Race	Gender	Tumor Stage	Maximum Dose of imatinib	Duration of rx prior to AE (days)	CAD/CAD Risk Factors	Potential Cardiac Adverse Event
1	32	W	M	Metastatic	800	55		Lower extremity edema
2	70	B	F	Metastatic	600	1588	CAD, HTN, CABG	Left ventricular dysfunction
3	57	B	F	Metastatic	400	91	HTN	Chest pain
4	54	B	M	Primary	800	11	HTN	Lower extremity edema
5	57	B	M	Primary	600	57	DM, hyperlipidemia	Acute coronary syndrome
6	54	W	M	Primary	600	17	CAD, PTCA, DM, hyperlipidemia, HTN,	Stable angina
7	77	B	F	Primary	400	338	DM, HTN, a-fib	Atrial fibrillation
8	21	W	F	Metastatic osteosarcoma	800	56		Pleural effusion
9	73	H	M	Metastatic	800	115	HTN	Ascites
10	41	W	M	Metastatic	400	303		Pulmonary edema
11	61	W	F	Metastatic	400	756	DM, HTN	Lower extremity edema
12	71	W	M	Metastatic	400	843	HTN	Acute coronary syndrome
13	88	W	M	Metastatic	400	320	PVD	Pulmonary edema, lower extremity edema
14	71	W	F	Metastatic	400	232	HTN	Pulmonary edema
15	74	W	F	Metatstatic	400	31		Lower extremity edema
16	81	W	M	Metastatic	400	1138	HTN, hyperlipidemia, PVD	Carotid stenosis
17	76	A	M	Metastatic	400	1517		Lower extremity edema
18	37	W	M	Primary	600	88		Pleural effusion

Abbreviations: CAD, coronary artery disease; HTN, hypertension; CABG, coronary artery bypass graft; DM, diabetes mellitus; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease