Contemporary Use of Digoxin in the Management of Cardiovascular Disorders

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Digoxin Use in Cardiovascular Medicine: Past and Present

Digitalis is the oldest compound in cardiovascular medicine that continues to be used in contemporary clinical practice.1 Evidence supporting the beneficial effects of digoxin on hemodynamic, neurohormonal, and electrophysiological parameters has been accumulated from >200 years of clinical experience and research (Table 1).2

Digoxin was approved for heart failure in 1998 under current regulations by the Food and Drug Administration on the basis of the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED), Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme (RADIANCE), and Digitalis Investigators Group (DIG) clinical trials.3-5 It was also approved for the control of ventricular response rate for patients with atrial fibrillation. The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend digoxin for symptomatic chronic heart failure for patients with reduced systolic function (Class IIa recommendation: weight of evidence/opinion is in favor of usefulness/efficacy), preserved systolic function (Class IIb: usefulness/efficacy is less well established by evidence/opinion), and/or rate control for atrial fibrillation with a rapid ventricular response (Class IIa).6 The new Heart Failure Society of America guidelines for heart failure provide similar recommendations.7

Despite its relatively recent approval by the Food and Drug Administration and the guideline recommendations, digoxin use is decreasing in patients with heart failure.8 In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry, only 30% of patients with left ventricular systolic dysfunction were being treated with digoxin before admission. Digoxin was added in only 8% of patients before discharge despite the fact that they had signs and symptoms of heart failure while receiving diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs) and β-blockers.9,10 This decrease in digoxin use is likely the result of several factors. Digoxin has not been promoted by the pharmaceutical industry and has received little attention at national and international meetings. This may have been the result of the development and introduction of life-saving therapies for heart failure, including β-blockers, ARBs, aldosterone blockers, and cardiac resynchronization therapy (CRT). Safety concerns about digoxin therapy—increased mortality in women also may have contributed to this decrease in its use.8,11

This update reevaluates the role of digoxin in the context of recent advances in heart failure therapy, provides practical recommendations for its use, and identifies areas for future research.

Clinical Evidence

Heart Failure

Digoxin possesses many characteristics of a beneficial drug for heart failure. It is the only oral inotrope that does not increase long-term mortality in chronic heart failure and has few side effects when dosed appropriately on the basis of serum concentration.2 Digoxin does not lower blood pressure or adversely affect renal function or electrolytes.2 Accordingly, it is easy to use in combination with other heart failure therapies, including ACE inhibitors or ARBs, β-blockers, and aldosterone antagonists. Digoxin is a very low-cost drug. This last aspect is particularly important in developing countries where patients may not be able to afford branded products and device therapies.

Several clinical trials conducted with digoxin provide compelling evidence supporting its use in the treatment of symptomatic chronic heart failure.2-5 PROVED was a 12-week placebo-controlled, digoxin-withdrawal study. This study enrolled patients in sinus rhythm with reduce systolic function and stable heart failure symptoms who were receiving digoxin and diuretics.3 Patients in whom digoxin was discontinued had a 2-fold increase in worsening heart failure and a decrease in both exercise capacity and LVEF compared with patients who continued on digoxin therapy.

The RADIANCE trial followed a similar protocol; however, patients were receiving ACE inhibitors in addition to diuretics and digoxin.4 Digoxin discontinuation was associated with a 6-fold increase in worsening heart failure, despite the fact that ACE inhibitors and diuretics were continued after its withdrawal. Functional capacity worsened in the withdrawal group, as did quality of life and ejection fraction (Table 2).4,12

A pooled analysis of the RADIANCE and PROVED trials suggested that triple therapy with digoxin, an ACE inhibitor,
and a diuretic was associated with the lowest risk of worsening heart failure (<5%). The rate of worsening heart failure was 19% among patients treated with digoxin and diuretics, 25% among patients receiving ACE inhibitors and diuretics, and 39% among patients receiving diuretics alone (Figure 1). In the separate analysis of the same database, a significant cost reduction related to hospitalizations was associated with digoxin therapy.

The DIG trial was a large, relatively simple NIH-sponsored trial designed to evaluate mortality in patients in sinus rhythm with reduced (DIG-Main) or preserved (DIG-Ancillary) systolic function. The study randomized 7788 patients. Patients were treated with ACE inhibitors and diuretics and were followed up for 3 years. The DIG main study included 6800 patients with an LVEF of <45%. Although digoxin did not reduce overall mortality, it did reduce heart failure–related death or hospitalization (Figure 2). Although this was not a prespecified outcome, deaths presumed to result from arrhythmia without evidence of worsening heart failure and from atherosclerotic coronary disease were apparently higher (15% versus 13%) in the digoxin group compared with placebo. At a 2-year follow-up, a reduction in total mortality and total hospitalization was demonstrated in a prespecified subgroup analysis of patients with an LVEF <25%, cardiothoracic ratio >55%, or NYHA class III/IV symptoms. In these subgroups, the relative reduction in heart failure mortality or heart failure–related death or hospitalization was 39% for patients with LVEF <25%, 35% for patients with cardiothoracic ratio >55% on chest x-ray, and/or 35% for patients with severe symptoms (Figure 3). The use of new or increasing doses of existing medications and/or open-label digoxin for worsening heart failure was greater in the placebo group. In this trial, 50% of patients were taking digoxin for the first time. Although this group had a much lower mortality, the magnitude of clinical improvement was similar compared with patients taking digoxin before randomization. During the study period, the proportion of patients hospitalized for digoxin intoxication was 2% in the digoxin compared with 0.9% in the placebo group.

Serum Concentration

The DIG trial did not show a reduction in all-cause mortality in patients treated with digoxin. Patients received doses to achieve SDC in the range of 0.5 to 2 ng/mL. Some patients achieved SDCs higher than is currently recommended (0.5 to 0.9 ng/mL). Several analyses suggest that the benefits of digoxin can be obtained with doses resulting in SDCs of <1 ng/mL.

The benefits from digoxin may be related not only to its hemodynamic effects but also to its ability to improve the neurohormonal profile. Improvements in neurohormonal profile and hemodynamics occur at low digoxin doses, and increasing the dose does not always result in further improvements in these measures. In the PROVED and RADIANCE studies, the clinical benefits were similar in patients with lower (serum concentration <1 ng/mL) and higher SDCs. A recent comprehensive post hoc analysis of the DIG trial that included all patients (preserved or reduced systolic function) suggested a survival benefit for patients with SDCs <1.0 ng/mL (Figure 4). Heart failure hospitalizations were reduced regardless of SDC. However, it should be emphasized that those findings are retrospective in nature and should be confirmed by prospective studies. Evaluated collectively, the available data suggest that higher digoxin doses resulting in serum concentrations that were considered therapeutic in the past (between 1 and 2 ng/mL) are not associated with further improvement in hemodynamics or neurohormones and may actually increase mortality. In contrast, digoxin dosed to achieve SDCs in the range of 0.5 to 0.9 ng/mL appears to be safe; improves left ventricular function, hemody-
namics, and neurohormonal profiles; reduces hospitalization; and possibly improves survival.\textsuperscript{16–20}

**Digoxin in Women**

Digoxin has not been well studied in women with heart failure even though they represent $\geq 50\%$ of all admissions for this condition.\textsuperscript{10} In the DIG trial, women made up only 22\% of the study population. One post hoc analysis of the DIG database suggested that women randomized to digoxin had increased all-cause mortality.\textsuperscript{11} However, subsequent independent analyses of the same database showed no evidence of increased mortality in women with a serum concentration $\leq 1.0$ ng/mL.\textsuperscript{21} A higher risk of mortality (but not hospitalization) was observed only in women with SDCs $>1$ ng/mL.\textsuperscript{21} An analysis of patients treated with digoxin in the Studies of Left Ventricular Dysfunction (SOLVD) database also failed to demonstrate a survival difference based on gender.\textsuperscript{22}

**Digoxin in the Elderly**

The incidence and prevalence of heart failure increase progressively with age. The mean age of patients hospitalized with heart failure is 75 years.\textsuperscript{9,10} Advanced age may predispose patients to an increased risk for digoxin intoxication that is related to decreased renal function, low lean body mass, and electrical conduction abnormalities.\textsuperscript{2} In the DIG trial, however, advanced age was not associated with an increased risk of digoxin intoxication.\textsuperscript{23} The beneficial effects of digoxin were found to be similar across all age groups regardless of LVEF.\textsuperscript{23} These findings demonstrate that digoxin remains a useful agent in elderly heart failure patients when variables such as lean body mass and renal function are taken into account.

**Preserved Systolic Function**

Approximately 50\% of patients hospitalized for acute heart failure syndromes have relatively preserved systolic func-
These patients are older and more likely to have a history of hypertension and atrial fibrillation. To date, only 2 relatively large studies have been conducted in heart failure patients with preserved systolic function: DIG-Ancillary and Effects of Candesartan in Patients With Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction or (CHARM-Preserved study). The effect of digoxin in 988 patients with heart failure and preserved systolic function (mean LVEF, 55%) was examined in the ancillary component of the DIG trial. The addition of digoxin to ACE inhibitors and diuretics resulted in a nonsignificant 12% reduction in heart failure mortality or heart failure hospitalizations. The direction and magnitude of this finding are similar to that observed in patients with decreased systolic function. In comparison, in CHARM-Preserved, therapy with candesartan resulted in an 11% relative risk reduction in cardiovascular death or heart failure hospitalization in patients with heart failure and preserved systolic function. In this trial, however, patients randomized to candesartan developed more hypotension, worsening renal function, and hypokalemia compared with the placebo group.

**Acute Heart Failure Syndromes**

Hospitalizations for worsening heart failure are a major problem in the United States, with almost 1 million hospitalizations occurring annually. This is associated with a readmission rate as high as 30% within 2 months after discharge. To date, no single agent used to improve presenting symptoms has been shown to be safe and effective. These include nesiritide, milrinone, tezosentan, and levosimendan. The effects of intravenous digoxin, alone or in combination with other vasodilators, are seen within an hour of its administration and result in increased

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**Figure 3.** Effect of digoxin in high-risk subgroups after 2 years of follow-up in the DIG trial. Data derived from the Digi-talis Investigation Group.

**Figure 4.** Mortality and hospitalization rates adjusted for multiple baseline variables in the DIG trial at 2 years in patients with a serum digoxin concentration of 0.5 to 0.9 ng/mL and >1 ng/mL. Data derived from Ahmed et al.
cardiac output, decreased pulmonary wedge pressure, increased ejection fraction, and improved neurohormonal profile without changes in blood pressure.\cite{31,32} This therapy may be continued during hospitalization and after discharge. Despite its potential benefits, no study to date has evaluated digoxin in the setting of acute heart failure. Accordingly, digoxin is not recommended for the management of acute heart failure syndromes by the ACC/AHA heart failure guidelines.\cite{6} However, given its acute positive hemodynamic effects and long-term safety data, digoxin should be evaluated in this setting by future trials.

Coronary Artery Disease
Myocardial ischemia may cause inhibition of the sodium-potassium pump, rendering myocardial tissue more sensitive to the arrhythmogenic effects of digoxis, even at lower doses.\cite{2} In a retrospective analysis, digoxin has been associated with an increase in postdischarge mortality in patients surviving myocardial infarction.\cite{6} However, in other studies, regression analysis failed to show that digoxin is an independent predictor of increased mortality. In the DIG trial, 70% of patients had ischemic heart disease, 65% had a history of myocardial infarction, and 30% had angina at the time of enrollment. Patients with an ischemic origin had a reduction in heart failure–related death or hospitalization similar to that seen in nonischemic patients.\cite{7} The DIG trial, however, did not examine the effects of digoxin in the settings of acute coronary syndromes. Because its safety has not been evaluated in this setting, digoxin should be avoided if possible during acute myocardial infarction or in patients with ongoing ischemia.

Digoxin in Contemporary Heart Failure Management
Digoxin Discontinuation
The recent ACC/AHA guidelines suggest that if a patient is taking digoxin but not ACE inhibitors or β-blockers, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted.\cite{6} The RADIANCE and PROVE studies showed a significant rate of clinical deterioration when digoxin was discontinued in stable patients with heart failure and a reduced systolic function in patients who were not taking a β-blocker.\cite{3,4} Digoxin may be discontinued, however, in patients who no longer have symptoms of heart failure, are in sinus rhythm, and have a significant improvement in systolic function while receiving ACE inhibitors and β-blocker.

Non–Potassium-Sparing Diuretics
Retrospective analyses suggest that chronic use of non–potassium-sparing diuretics may be harmful in heart failure, particularly when higher doses are used for worsening symptoms.\cite{33,34} Because digoxin improves heart failure symptoms, its use may reduce the need for increased doses of non–potassium-sparing diuretics.\cite{5} In the DIG trial, patients randomized to digoxin were less likely to need cointerventions, including increased doses of diuretics for worsening heart failure.\cite{5,16,26}

### β-Blocker Therapy
The DIG study was conducted before β-blockers were proved conclusively to reduce mortality and morbidity in heart failure. Most patients enrolled in trials of β-blockers, however, were receiving digoxin (Table 3). It is not known if the findings of β-blocker trials would have been similar without background digoxin therapy. Data from the US Carvedilol Trial and Australia/New Zealand Trial suggest a similar reduction in mortality and hospitalization in patients treated with the combination of digoxin and carvedilol compared with either drug alone.\cite{35}

Pharmacological rationale exists for combining β-blocker and digoxin therapy. Ejection fraction may decline initially during β-blocker initiation.\cite{16} Digoxin improves hemodynamics and ejection fraction within hours of its administration.\cite{31,32} Digoxin may potentially prevent worsening hemodynamics during initiation of β-blocker therapy in patients with severe heart failure. Despite those theoretical considerations, the value of adding digoxin in patients already receiving a β-blocker for heart failure has not been well studied.

### Aldosterone Antagonists
Aldosterone antagonists improve survival in patients with severe heart failure and reduced systolic function.\cite{37} Subgroup analyses have shown that this mortality benefit is particularly evident in patients receiving digoxin therapy.\cite{37} Therefore, in severe heart failure, digoxin should be considered as an addition to aldosterone antagonists. It should be recognized that the benefits of aldosterone antagonists in mild to moderate heart failure or preserved systolic function have not been studied. These agents should not be used in patients with a serum creatinine >2.5 mg/dL or serum potassium >5.0 mEq/L.\cite{38}

### Angiotensin Receptor Blockers in Addition to ACE Inhibitors
The addition of ARB therapy to ACE inhibitors in heart failure and reduced systolic function does not appear to reduce mortality but has been associated with a decreased rate of worsening heart failure.\cite{39,40} In the CHARM-Added trial, the addition of candesartan to an ACE inhibitor resulted in a 15% reduction in the risk of CV death or heart failure hospitalization.\cite{40} In this trial, 23 patients had to be treated with candesartan to keep 1 patient from cardiovascular death.

### TABLE 3. Digoxin as Background Therapy in Heart Failure Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Receiving Digoxin as Background Therapy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol\cite{47}</td>
<td>91</td>
</tr>
<tr>
<td>COPERNICUS\cite{48}</td>
<td>67</td>
</tr>
<tr>
<td>MERIT-HF\cite{64}</td>
<td>64</td>
</tr>
<tr>
<td>CIBIS-II\cite{52}</td>
<td>75</td>
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<tr>
<td>RALES\cite{75}</td>
<td>64</td>
</tr>
<tr>
<td>CARE\cite{42}</td>
<td>45</td>
</tr>
<tr>
<td>SCD-HeFT\cite{61}</td>
<td>73</td>
</tr>
</tbody>
</table>

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TABLE 4. Practical Considerations for the Use of Digoxin

Situations in which digoxin should be considered:

Heart failure with reduced systolic function
- In patients in sinus rhythm or atrial fibrillation, regardless of age and gender, who continue to have signs and symptoms of heart failure despite standard therapies with ACE inhibitors or ARBs, β-blockers, and diuretics.
- In all patients with severe symptoms (NYHA class III or IV), cardiomegaly on chest X-ray (cardiothoracic ratio >0.55), or LVEF <25%.
- In patients with persistent heart failure symptoms despite the addition of aldosterone antagonists or ARB to an ACE inhibitor or CRT.
- Heart failure with preserved systolic function
  - In patients with symptoms not responding to other available therapies.

Atrial fibrillation
- In patients with rapid ventricular response despite therapy with a β-blocker.

Dosing considerations:
- No loading dose (except in atrial fibrillation with rapid ventricular response).
- Low doses (0.0625–0.25 mg/d) individualized on the basis of lean body weight, age, renal function, and concomitant medications.
- Therapeutic serum concentration of 0.5–1 ng/mL.

Monitoring:
- Indications for measurement of SDC
  - Suspected digoxin intoxication
  - Compliance
  - Conditions likely to alter SDC (see Table 6)
- Obtain SDC 7–14 days after therapy initiation.
- Serum level should be either a trough level or drawn no sooner than 8 h after dosing.
- SDC should be repeated if the patient’s clinical conditions change substantially (weight loss, worsening renal function, or addition/deletion/modification of an interacting medication).

TABLE 5. Causes of Altered Responsiveness to Digoxin

Increased resistance
- Apparent
  - Tablets not taken as prescribed
  - Inadequate bioavailability of tablets, inadequate intestinal absorption, increased metabolic degradation (eg, by gut flora)
- True end-organ resistance
  - Infancy
  - With respect to control of ventricular response in the presence of atrial fibrillation or atrial flutter
  - Fever
  - Elevated sympathetic tone from all causes, included uncontrolled congestive heart failure
  - Hyperthyroidism

Increased sensitivity
- Apparent
  - Unsuspected use of digoxin
  - Change from poorly absorbed tablets to well-absorbed tablets
  - Decreased renal excretion
  - Drug–drug interactions
  - True end-organ sensitivity to toxic effects
    - Cardiac amyloidosis
    - Active myocardial ischemia
    - Electrolyte imbalance (especially hypokalemia)
    - Acid-base imbalance
    - Concomitant drug administration (eg, catecholamines)
    - Hypothyroidism
    - Hypoxemia (especially in setting of acute respiratory failure)
    - Altered autonomic tone (eg, vagotonic states)

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QRS complex. Given that severe symptoms are the main indication for CRT therapy, digoxin therapy may be considered after CRT if symptoms persist.

Atrial Fibrillation

Atrial fibrillation is present in ~30% of heart failure patients. At rest, digoxin can effectively control the ventricular response in atrial fibrillation by enhancing vagal tone. However, it may be less effective at controlling the ventricular response during exercise or in the setting of enhanced sympathetic tone.

In patients with heart failure and reduced systolic function, the combination of digoxin and a β-blocker reduces symptoms, improves ventricular function, and leads to better rate control than either agent alone. The best strategy for rate control is a 2-drug combination, usually consisting of digoxin and a β-blocker. Using a β-blocker and digoxin in combination allows lower doses to be used, thus improving tolerability and decreasing the risk of toxicity. Diltiazem and verapamil also are options, but these agents should not be used in the setting of systolic dysfunction. Caution should be used when combination therapy with digoxin and amiodarone is chosen for rate control because amiodarone can significantly increase SDC.
Practical Considerations for Digoxin

Indications and Contraindications
Digoxin is indicated for the treatment of symptomatic heart failure and for the control of ventricular response in patients with atrial fibrillation (Table 4). It should generally be avoided in patients with sinus node disease, second- or third-degree AV block, accessory AV pathways (Wolff-Parkinson-White syndrome), cardiac amyloidosis, and hypertrophic cardiomyopathy. Digoxin should be used cautiously and with appropriate monitoring in patients with renal impairment, hypokalemia, hypomagnesemia, and hypothyroidism because these patients may be at higher risk of digoxin intoxication. It also should be used cautiously or not at all in patients with acute myocardial infarction or ongoing ischemia and in those undergoing electrical cardioversion.

Dosing Guidelines
Most heart failure patients achieve a serum concentration of 0.5 to 1.0 ng/mL with doses of 0.125 to 0.25 mg/d. However, SDC is determined by digoxin dose, age, gender, kidney function, use of diuretics, and/or use of concomitant drugs that are known to alter the SDC (eg, amiodarone).16 Thus, these factors should be taken into account when digoxin is prescribed. It may be recommended that adult men with clinically stable heart failure and normal renal function be prescribed a daily digoxin dose of 0.25 mg to achieve a therapeutic SDC <1 ng/mL. In heart failure patients who are elderly, are female, or have renal impairment, a daily dose of 0.125 mg would be more appropriate. For patients with multiple risk factors for high SDC, such as an elderly woman with impaired renal function, digoxin should be started at a daily dose of 0.0625 mg. Loading doses are unnecessary when digoxin is used to treat chronic heart failure. For atrial fibrillation, a loading dose of 0.5 to 0.75 mg, followed by a maintenance dose, is warranted when the rate is not controlled with β-blockers. To achieve chronic optimal rate control, β-blocker dose rather than digoxin dose should be adjusted. Intravenous digoxin should be used rarely, if at all.

Monitoring Serum Digoxin Concentration
Serum digoxin concentrations should be monitored to guide therapy in patients at high risk for developing digoxin intoxication (Table 4). An SDC should be obtained ~14 to 21 days after therapy initiation. The half-life of digoxin is ~2 days in patients with normal renal function and is prolonged to 4 to 7 days in patients with renal failure. Sampling for digoxin concentrations should be performed no sooner than 8 hours after the last dose. Samples obtained before this time period will reflect the distribution phase of digoxin, and they are inaccurate for clinical decision making. Once a steady-state digoxin concentration has been obtained, repeated measurements are not necessary unless the patient’s renal function changes, an interacting drug is added or removed, or a patient experiences substantial weight loss. Table 5 outlines the indications and procedures for measuring digoxin concentrations.

Drug Interactions
Several drugs interact with digoxin (Table 6). Patients receiving these drugs may need to have the digoxin dose adjusted.

Digoxin Intoxication
Cardiac manifestations of digoxin intoxication include sinoatrial block, AV block, ventricular bigeminy, tachycardia, and ventricular fibrillation. Noncardiac signs of digoxin toxicity include nausea, vomiting, visual disturbances, con-
fusion, and severe hyperkalemia. If an elevated SDC is detected in the absence of symptoms, the time that the laboratory sample was obtained should be verified. If the sample was obtained <6 hours after the last dose of digoxin, then the level may represent the distribution phase of digoxin. If the elevated SDC is thought to reflect digoxin intoxication, digoxin should be discontinued. Hypokalemia and hypomagnesemia also should be corrected. Intravenous calcium is contraindicated because it may precipitate life-threatening arrhythmias. In addition, other drugs that increase SDC or potentiate its effects also should be discontinued. Asymptomatic bradycardias should be closely monitored. Symptomatic patients with bradycardias should receive atropine. Patients with life-threatening arrhythmias should be given purified antidigoxin Fab fragments from digoxin-specific antisera (DIGIBIND). Once DIGIBIND is administered, SDCs should not be obtained until DIGIBIND has been cleared from the body. Patients presenting with severe hyperkalemia as a result of digoxin intoxication should undergo dialysis. Factors that may have contributed to intoxication (worsening renal function, drug interactions, etc) should be considered before therapy is reinitiated.

Conclusions
Digoxin reduces hospitalizations in patients with chronic heart failure. When combined with β-blockers, it remains a useful agent to achieve rate control in atrial fibrillation. This manuscript is dedicated to the memory of Drs Richard Gorlin and Thomas Smith, who were instrumental in clarifying the role of digoxin in clinical practice. The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

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Disclosures

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