Cardiovascular Drugs

Digitalis

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Abstract—Cardiac glycosides have played a prominent role in the therapy of congestive heart failure since William Withering codified their use in his late 18th century monograph on the efficacy of the leaves of the common foxglove plant (Digitalis purpurea). Despite their widespread acceptance into medical practice in the ensuing 200 years, both the efficacy and the safety of this class of drugs continue to be a topic of debate. Moreover, despite the fact that the molecular target for the cardiac glycosides, the α-subunit of sarcolemmal Na⁺K⁺-ATPase (or sodium pump) found on most eukaryotic cell membranes, has been known for several decades, it remains controversial whether the sympatholytic or positive inotropic effects of these agents is the mechanism most relevant to relief of heart failure symptoms in humans with systolic ventricular dysfunction. Herein, we review the molecular and clinical pharmacology of this venerable class of drugs, as well as the manifestations of digitalis toxicity and their treatment. We also review in some detail recent clinical trials designed to examine the efficacy of these drugs in heart failure, with a focus on the Digoxin Investigation Group data set. Although, in our opinion, the data on balance warrant the continued use of these drugs for the treatment of symptoms of heart failure in patients already receiving contemporary multidrug therapy for this disease, the use of digitalis preparations will inevitably decline with the maturation of newer pharmacotherapies. (Circulation. 1999;99:1265-1270.)

Key Words: drugs ■ digitalis ■ heart failure ■ pharmacology

Cardiac glycosides have played a prominent role in the therapy of congestive heart failure since William Withering codified their use in his late 18th century monograph on the efficacy of the leaves of the common foxglove plant (Digitalis purpurea) in 1785. Nevertheless, throughout this century, a controversy has existed about whether the risks of digitalis preparations outweigh their benefits, particularly in patients with heart failure in sinus rhythm. In this review, we begin with a brief overview of the basic and clinical pharmacology of the cardiac glycosides, followed by an examination of recent clinical trials that have studied the use of digoxin in patients with moderate to severe congestive heart failure. The terms “digitalis” or “cardiac glycosides” are used throughout to refer to any of the steroid or steroid glycoside compounds that exert characteristic positively inotropic and electrophysiological effects on the heart. In the 1990s, digoxin is by far the most commonly prescribed of these drugs owing to the ready availability of techniques for measuring its levels in serum, flexibility in routes of its administration, and its intermediate duration of action. Detailed descriptions of sources of cardiac glycosides, their chemistry, and structure-activity relationships are extensively considered in standard texts.

Mechanism of Action

Positive Inotropic Effect

By the late 1920s, it became clear that digitalis preparations caused a positive inotropic effect on the intact ventricle, resulting in an increase in the rate of rise of intracavitary pressure during isovolumic systole at constant heart rate and aortic pressure that could be demonstrated in normal as well as failing cardiac muscle. Cardiac glycoside administration caused the ventricular-function (Frank-Starling) curve of the intact heart to shift upward and to the left, so that more stroke work would be generated at a given filling pressure. These effects appear to be sustained during in vivo administration of digitalis, for periods of weeks to months, without any evidence of desensitization or tachyphylaxis. It is now generally believed that digitalis compounds bring about an increase in the availability of activator Ca²⁺ in heart cells and that this increase in intracellular Ca²⁺ activity is sufficient to explain both the inotropic and arrhythmogenic effects of these drugs.

All cardioactive steroids share the property of being potent and highly specific inhibitors of the intrinsic membrane protein Na⁺K⁺-ATPase. This enzyme comprises the cellular “sodium pump,” in which membrane ion translocation is coupled to the hydrolysis of a high-energy ATP phosphate. Indeed, Jens Skou was awarded the 1997 Nobel prize in chemistry for his discovery in the 1960s of the enzymatic activity he termed the Na⁺K⁺-ATPase, which he characterized in the giant neurons of shellfish. The enzyme is a heterotrimer consisting of α-, β-, and γ-subunits, the α-subunit of which contains the Na⁺, K⁺, and ATP binding sites of the intact enzyme, and has been highly conserved in

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This review is dedicated to the memory of Richard N. Gorlin, MD, and Thomas W. Smith, MD.

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eukaryotes for the establishment and maintenance of transmembrane Na\(^+\) and K\(^+\) gradients (see Reference 5 for a review).

Another enduring characteristic of Na\(^+\)K\(^+\)-ATPase that is unique among the P-type ATPases is the presence of a binding site on the extracytoplasmic face of the \(\alpha\)-subunit for the cardiac glycosides. Indeed, the highly selective action of the cardiac glycosides to bind to the “digitalis binding site” on Na\(^+\)K\(^+\)-ATPase has engendered much speculation about the possible existence of endogenous ligands, simply because the amino acid sequence and conformation that form their binding site have been so highly conserved over many phyla and millennia. Although intriguing data exist (reviewed in References 6 through 9), there is as yet no proof that any “endogenous digitalis” exists that has a well-defined biological role in regulating Na\(^+\)K\(^+\)-ATPase activity.

Compelling direct evidence supporting cardiac glycoside–induced increases in intracellular Na\(^+\) concentration or activity ([Na\(^+\)]) has now been obtained, and the mechanism of digitalis-induced positive inotropy is known to involve an altered balance between intracellular Na\(^+\) and Ca\(^2+\). The transmembrane Na\(^+\) influx occurring with each action potential, in the presence of diminished outward Na\(^+\) pumping due to digitalis, leads to an increase in intracellular Na\(^+\) concentration that in turn increases intracellular Ca\(^{2+}\) stores, either through enhanced Ca\(^{2+}\) entry, reduced Ca\(^{2+}\) efflux, or both, effects that are thought to be mediated via Na\(^+\)-Ca\(^{2+}\) exchange. Interestingly, recent evidence suggests that the immediate positively inotropic effect of cardiac glycosides, measured either in the intact heart in a conscious dog model or in isometrically contracting papillary muscle strips, is achieved with remarkable energy transfer efficiency and little oxygen wasting.\(^10\) Finally, Santana and colleagues\(^11\) have recently demonstrated that physiologically relevant (ie, nanomolar) concentrations of cardiac glycosides can alter the ion selectivity of voltage-sensitive Na\(^+\) channels in sarcolemmal and T-tubular membranes, permitting Ca\(^{2+}\) entry by a mechanism they have termed “slip-mode conductance.” The relevance of this finding to the mechanism of action of these drugs will require further study.

**Electrophysiological Effects**

As with the positive inotropic effect of these drugs, the major effect on cardiac rhythm of digitalis preparations is believed to be due to inhibition of the sodium pump. However, cells in various parts of the heart show differing sensitivities to digitalis, and both direct and neurally mediated effects are now known to occur. Indeed, at therapeutic levels of digoxin, these drugs decrease automaticity and increase maximum diastolic potential, effects that can be blocked by atropine, whereas higher (toxic) concentrations decrease diastolic potentials and increase automaticity.

Similarly, the toxic arrhythmogenic effects of the cardiac glycosides are due to a combination of direct effects on the myocardium and neurally mediated increases in autonomic activity. Both systolic and diastolic [Ca\(^{2+}\)], increase during digitalis-induced arrhythmias, increases that were first inferred from changes in tension, leading to the idea that intracellular “Ca\(^{2+}\) overload” contributes to the observed arrhythmogenic effects. Spontaneous cycles of Ca\(^{2+}\) release and reuptake then ensue, resulting in afterdepolarizations and aftercontractions. The afterdepolarization is the result of a Ca\(^{2+}\)-activated transient inward current (\(I_{\text{Ca}}\)) and is thought to be the macroscopic manifestation of Ca\(^{2+}\)-activated nonspecific cation channels, plus Na\(^+\)-Ca\(^{2+}\) exchange current.

**Neurally Mediated Actions of Cardiac Glycosides**

It is important to understand the role of digitalis glycosides in modifying the abnormal autonomic nervous system activity characteristic of advanced heart failure, including altered baroreflex activity. Mason and Braunwald\(^12\) noted more than 30 years ago that intravenous ouabain increased mean arterial pressure, forearm vascular resistance, and venous tone in normal human subjects, probably in part because of direct but transient effects on vascular smooth muscle. In contrast, as shown in the Figure, patients with heart failure responded with a decline in heart rate and other effects that were consistent with enhanced baroreflex responsiveness. More recently, Ferguson et al\(^13\) demonstrated in patients with moderate to severe heart failure that infusion of deslanoside, a rapidly acting cardiac glycoside, increased forearm blood flow and cardiac index and decreased heart rate concomitantly with a marked decrease in skeletal muscle sympathetic nerve activity measured as an indicator of centrally mediated sympathetic nervous system activity. In contrast, dobutamine, a sympathomimetic drug that increased cardiac output to a similar degree, did not affect muscle sympathetic nerve activity in these patients. On the basis of these observations and those of others (reviewed in detail in Reference 14), reduced sympathetic nervous system activation may be an important mechanism contributing to the efficacy of cardiac glycosides in the treatment of patients with heart failure (and may occur at blood levels of these drugs that are below those necessary to achieve a direct inotropic effect).

**Clinical Pharmacology**

**Digoxin Dosing**

Although a number of cardiac glycoside preparations remain available, digoxin is the most commonly prescribed, and its pharmacology will be described in detail. The reader is referred to comprehensive texts for a description of the pharmacology of other cardiac glycosides that remain in clinical use.\(^3\) Digoxin is excreted exponentially, with an elimination half-life of 36 to 48 hours in patients with normal renal function, resulting in the loss of about one third of body stores daily. Renal excretion of digoxin is proportional to the glomerular filtration rate (and hence to creatinine clearance).

With daily maintenance therapy, a steady state is reached when daily losses are matched by daily intake. For patients not previously given digoxin, institution of daily maintenance therapy without a loading dose results in development of steady-state plateau concentrations after 4 to 5 half-lives, or 7 to 10 days, in subjects with normal renal function. If the elimination rate of the drug is prolonged, the length of time before a steady state is reached on a daily maintenance dose would also be prolonged proportionately. A patient’s estimated lean body mass should be used in the calculation for maintenance dosing. Also, recent evidence suggests that the
steady-state volume of distribution of digoxin ($V_{dss}$) is decreased in chronic renal failure, and therefore loading doses of digoxin as well as maintenance doses should be decreased in these patients. Digoxin doses in neonates and infants are substantially larger than those in adults, resulting in relatively higher serum digoxin concentrations, which are generally well tolerated. Digoxin does cross the placenta, and fetal umbilical cord venous blood levels of the drug are similar to maternal blood levels. There is no contraindication for use of digoxin during pregnancy or during lactation.

There is usually no need to treat patients with a loading dose of digoxin except in the setting of certain supraventricular arrhythmias when other drugs useful in treating these arrhythmias are contraindicated or have not been effective. This is due to the narrow therapeutic “window” of cardiac glycosides, which often makes it difficult to judge accurately an effective loading dose of digoxin that will also minimize the risk of toxicity. Often, the patients who would benefit most from the addition of a cardiac glycoside are also those at greatest risk of exhibiting toxic effects of these drugs (see below). Because the mechanism of action of the cardiac glycosides relevant to their beneficial effects in heart failure patients remains controversial, there is debate about the appropriate therapeutic range for digoxin. Our analysis of the consensus to date, based on clinical trial data reviewed below, would put that range between 0.5 and 1.5 ng/mL.

**Drug Interactions**

Concomitant drug administration may directly alter the pharmacokinetics of digitalis preparations or indirectly alter their action on the heart by pharmacodynamic interactions. Quinidine reduces both the renal and nonrenal elimination of digoxin and also decreases its volume of distribution. Recent evidence indicates that quinidine inhibits digoxin transport across epithelial cell membranes (particularly in the kidney) owing to its high affinity for P-glycoprotein, an ATP-dependent efflux pump encoded by the $mdr1a$ gene. Amiodarone administration has been found to increase the steady-state digoxin concentration, and maintenance doses of digoxin should be decreased by $\pm 50\%$. Newly introduced drugs will require close surveillance for interactions with cardiac glycosides.

Examples of pharmacodynamic interactions include concomitantly administered diuretic agents that may increase the incidence of digitalis toxicity both by decreasing the glomerular filtration rate owing to volume depletion and by inducing a variety of electrolyte disturbances, including hypokalemia, hypomagnesemia, and (for thiazide diuretics) hypercalcemia. Also, concurrent administration of some antiarrhythmic agents may increase the possibility of proarrhythmic events, and venous tone declined in patients with advanced heart failure after intravenous ouabain. The response in normal subjects is likely due in part to a direct effect of cardiac glycosides on peripheral vascular tone, whereas the rapid, opposite hemodynamic effect in heart failure patients is believed to be due to a decline in sympathetic nervous system activity, mediated by enhanced sensitivity of the baroreflex response. Adapted from Mason and Braunwald, with permission.

Cardiac glycosides and peripheral vascular resistance in heart failure. A, In a series of pioneering studies, Mason and Braunwald noted that a 10-minute intravenous infusion of ouabain, a hydrophilic, rapidly acting cardiac glycoside, into normal subjects increased mean arterial pressure as well as forearm vascular resistance and venous tone, as shown in this representative example. However, as shown in B, forearm vascular resistance and venous tone declined in patients with advanced heart failure after intravenous ouabain. The response in normal subjects is likely due in part to a direct effect of cardiac glycosides on peripheral vascular tone, whereas the rapid, opposite hemodynamic effect in heart failure patients is believed to be due to a decline in sympathetic nervous system activity, mediated by enhanced sensitivity of the baroreflex response. Adapted from Mason and Braunwald, with permission.
Digitalis

Digitalis Toxicity

Electrophysiological Abnormalities

ECG manifestations of digitalis toxicity, such as premature ventricular contractions, are numerous but, unfortunately, too nonspecific in most instances to be diagnostic. At higher doses, junctional pacemakers may begin to discharge at increasing frequency, resulting in a nonparoxysmal AV junctional tachycardia. This is recognized clinically as a paradoxical regularization of the ventricular rate despite persistent atrial fibrillation. Common supraventricular arrhythmias associated with digitalis toxicity include tachycardias that originate due to enhanced atrial automaticity. Although there is no single ECG abnormality that is pathognomonic of digitalis excess, the combination of enhanced automaticity and impaired conduction (eg, AV block accompanied by an accelerated junctional pacemaker) is highly suggestive of toxicity even in patients whose serum levels are within the accepted therapeutic range.

The enhanced automaticity of cardiac tissue in response to toxic levels of cardiac glycosides is increased by hypokalemia in experimental animals, whereas the appearance of delayed afterdepolarizations that could reach threshold is antagonized by hyperkalemia. However, hyperkalemia may lead to exacerbation of digitalis-induced conduction delays, particularly in the AV node. Finally, elevated serum Ca$^{2+}$ levels increase ventricular automaticity, and this effect is at least additive to, and perhaps synergistic with, the effects of digitalis. Administration of intravenous calcium parenterally to patients to whom digitalis has been given may provoke lethal ventricular arrhythmias.

Treatment of Digitalis Toxicity

The key to successful treatment is early recognition that an arrhythmia is related to digitalis intoxication. The more common manifestations (including occasional ectopic beats, marked first-degree AV block, or atrial fibrillation with a slow ventricular response) require only temporary withdrawal of the drug and ECG monitoring. Ventricular tachycardia due to digitalis intoxication demands immediate vigorous treatment. Sinus bradycardia, sinoatrial arrest, and second- or third-degree AV block are often treated effectively with atropine, although pacing may be required. Administration of potassium salts is recommended for ectopic ventricular arrhythmias, even when the serum potassium is within the “normal” range. Hemodialysis is ineffective in the treatment of digoxin toxicity owing to the drug’s large volume of distribution (averaging 4 L/kg).

Although several antiarrhythmic drugs have been used in the treatment of digitalis-induced ventricular arrhythmias, the first-line treatment for life-threatening digitalis toxicity is now the administration of digoxin-specific antibody fragments. The widespread availability of Fab fragments of high-affinity, polyclonal, digoxin-specific antibodies provides the clinician with a means of rapidly and selectively reversing digitalis toxicity with little risk of adverse effects. A number of patients have now been treated with antidigoxin Fab fragments on ≈2 occasions without incident.

Digoxin in Supraventricular Tachycardia

As reviewed above, the principal mechanism by which cardiac glycosides slow the ventricular response in supraventricular tachycardias is by decreasing sympathetic nervous system activity (particularly in patients with heart failure) and by enhancing parasympathetic nervous system activity. The role of digoxin in paroxysmal atrial fibrillation, a condition in which the drug has limited efficacy, has been superseded by the introduction of newer, more efficacious, and safer drugs over the past 2 decades. The only patients with supraventricular tachycardia for whom cardiac glycosides remain useful adjunctive therapy are those with atrial fibrillation (acute and chronic) and symptomatic ventricular systolic dysfunction. Even in this population, digoxin is typically sufficient for ventricular rate control only in patients with relatively well-compensated heart failure at rest (ie, in the absence of markedly enhanced sympathetic nerve system activity).

Safety and Efficacy in Heart Failure: The Clinical Trial Data

Relevance of Serum Digoxin Levels

Recent data from some clinical trials, reviewed below, suggest that the sympatholytic effects of digoxin may occur at serum drug concentrations below those necessary to achieve a classic positively inotropic effect (note that we term these actions of digoxin a “sympatholytic” effect and avoid the commonly used, but overly vague and often incorrect, appellation “neurohormonal antagonist,” because many factors included under this umbrella, such as angiotensins, endothelins, and inflammatory cytokines, to name a few, are neither neurally derived nor hormones in the conventional sense). Gheorghiade et al20 showed that increasing the dose from a mean of 0.2 to 0.39 mg/d (corresponding to an increase in serum levels from 0.67 to 1.22 ng/mL) resulted in an increase in ejection fraction but no further change in exercise tolerance or decline in venous norepinephrine levels, a conclusion supported by at least several additional small clinical trials (eg, Reference 21; reviewed in Reference 14).

The possibility that digoxin could exhibit several mechanisms of action over the range of serum concentrations achieved clinically could explain why patients with high digoxin levels (>1.1 ng/mL) had a higher mortality in a clinical trial designed to study the effect of milrinone on survival in heart failure patients (the Prospective RandOmized Milrinone Survival Evaluation [PROMISE]), an effect that was independent of ejection fraction.22 Therefore, judicious use of digitalis requires recognition of concomitant medications or disease states that could affect digoxin pharmacokinetics, as well as early recognition of potential toxicity, both of which remain essential for safe and effective dosing of this class of agents.

Smaller Clinical Trials in Patients With Heart Failure

A number of short- and long-term controlled and uncontrolled clinical trials have suggested that digoxin results in an impres-
A number of lingering controversies over the role of digoxin were to be resolved by the large multicenter Digitalis Investigation Group (DIG) trial, composed of 2 studies in a total of 302 centers in the United States and Canada. The “main” trial required patients to be in sinus rhythm, with documented left ventricular ejection fraction ≤0.45 and heart failure as determined by preset signs, symptoms, or radiographic criteria. Prior or ongoing therapy with digoxin was admissible; therefore, in effect, the DIG trial was in fact a digoxin-withdrawal trial.

The use of ACE inhibitors was not mandated but “strongly encouraged”; additional drugs could be added at the discretion of the investigator, and follow-up was established at 4 weeks, 4 months, and then every subsequent 4 months. The primary end point was all-cause mortality, and secondary end points were mortality due to cardiovascular causes, mortality due to worsening heart failure, and hospitalization due to worsening heart failure or other causes. Among the 6800 patients enrolled in this main trial, there were no differences in baseline characteristics between active-drug and placebo group, including demographics, cause of heart failure, ejection fraction, dose of digoxin (or placebo) used, or use of ACE inhibitors, nitrates, or diuretics.

After a mean follow-up of 37 months (range, 28 to 58 months), there were no differences in all-cause or cardiovascular mortality. There was a trend toward a reduction in death from heart failure, with a relative risk of 0.88 (95% CI, 0.77 to 1.01). The pivotal difference between the digoxin and placebo groups is to be found in the decreased risk of hospitalization for heart failure, with a relative risk for patients taking digoxin of 0.72 (95% CI, 0.66 to 0.79) (Table). This effect was sufficiently large that it remained statistically significant when combined with the mortality end points. The reduction in relative risk was greater for patients with ejection fractions <25% and for patients with more advanced symptoms, as measured by NYHA classification. The heart failure survival and hospitalization curves appear to separate early after randomization, especially in the patient subgroup in which digoxin was withdrawn, supporting the conclusions reached in PROVED and RADIANCE.

Open-label digoxin was given to more patients taking placebo than digoxin (22.0% versus 14.2%). In the subgroup of patients with recorded digoxin levels, >88% were within the prescribed therapeutic range of 0.5 to 2.0 ng/mL at 1 month. Overall, there were nearly 10% fewer total cardiovascular hospitalizations (1694 or 49.9% versus 1850 or 54.4%) as well as fewer hospitalizations for each digoxin-treated patient. In addition, the reduction in risk of death or need for hospitalization due to worsening heart failure was the same for patients taking digoxin at the time of randomization and those not previously treated with the drug.

Despite these encouraging results, an increase in deaths from other cardiac causes was noted in the group randomized to receive digoxin. This category included deaths presumed to result from tachyarrhythmias or bradyarrhythmias without worsening heart failure, as well as deaths due to atherosclerotic coronary disease, low-output states, and cardiac surgery. Out-of-hospital death presumed to be due to an arrhythmia was not a prespecified end point, and no data have been published from the trial for this separate group.

Hence, despite the comprehensive data set that emerges from the DIG trial, our ability to resolve all outstanding controversies with digoxin using the DIG trial data set is limited. The question of an “ideal” (ie, most efficacious and least toxic) serum digoxin

### Table: Relative Risk Reduction in Hospitalizations With Digoxin Therapy

<table>
<thead>
<tr>
<th>Reason for hospitalization</th>
<th>Digoxin (n=3397), n (%)</th>
<th>Placebo (n=3403), n (%)</th>
<th>Absolute Difference, %</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cardiovascular</td>
<td>1694 (49.9)</td>
<td>1850 (54.4)</td>
<td>-4.5</td>
<td>0.87 (0.81–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>910 (26.8)</td>
<td>1180 (34.7)</td>
<td>-7.9</td>
<td>0.72 (0.66–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Suspected digoxin toxicity</td>
<td>67 (2.0)</td>
<td>31 (0.9)</td>
<td>1.1</td>
<td>2.17 (1.42–3.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of patients hospitalized</td>
<td>2184 (64.3)</td>
<td>2282 (67.1)</td>
<td>-2.8</td>
<td>0.92 (0.87–0.98)</td>
<td>0.006</td>
</tr>
<tr>
<td>No. of hospitalizations</td>
<td>6356</td>
<td>6777</td>
<td></td>
<td></td>
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</tbody>
</table>

Adapted from the Digitalis Investigation Group.27
level remains unresolved. Furthermore, in an ancillary study of the DIG trial, a subgroup of 581 patients from both the main and secondary studies (ejection fraction ≤0.45 and >0.45, respectively) completed 6-minute corridor walk tests and a variety of quality-of-life questionnaires at enrollment and at 1, 4, and 12 months. No statistically significant differences were detected between the digoxin and placebo groups (Rekha Garg, MD; personal communication, 1998), although it is possible that this substudy was underpowered to detect meaningful differences among the most symptomatic patients.

Finally, any assessment of the likelihood that digoxin will remain a mainstay of standard heart failure therapy is further complicated by the emergence of agents that act directly to suppress the activity of the sympathetic nervous system in heart failure, particularly the β-adrenergic antagonists. It is unlikely that another study will be performed to resolve the outstanding clinical issues in the post-DIG trial era. The effort and costs required to enroll patients in a non–industry-sponsored trial of a generically available drug with sufficient power are prohibitive. Furthermore, as standard drug therapy for heart failure improves, a larger number of patients will be required to show an effect on survival. In the setting of the maturation of newer therapies that focus on survival as the important outcome, the likelihood is that the digoxin debate, as well as the usage of this venerable class of drugs, will fade in intensity, albeit without a clear declaration of victory by proponents or detractors.

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