RESEARCH ARTICLE

Is digitalis currently useful for heart failure treatment?

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Abstract

Foxglove has been used for over 200 years to reduce water retention in its early days; Since the end of the 19th century, the treatment of heart failure has shown good clinical results. At the beginning of the 20th century, the treatment of heart failure began with good results and in the middle of the century scientific studies were carried out to determine the direct effects on the heart. 10 years later, clinical experience and technological advances demonstrated a really good efficacy that the digitalis effect had for the failing heart, with a defect: it is an old drug that appears obsolete for its current management in the presence of great new drugs that have proven useful in heart failure.
From the last third of the 20th century, it was shown that the heart benefits from the combination are better than the drugs alone, so digitalis has a role that, in combination with the other drugs, significantly enhances the beneficial effects for the treatment of heart failure.

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I - Origin of the use of digitalis medication.

Digitalis treatment has been used for over 200 years to reduce water retention in its early days; Since the end of the 19th century, the treatment of heart failure has shown good clinical results. At the beginning of the 20th century, the treatment of heart failure began with good results and in the middle of the century scientific studies were carried out to determine the direct effects on the heart. As we know, digitalis has been used for more than 200 years treatment of this disease, but obviously there were no other drugs besides diuretics that could have actions that would justify its use; in 1920 the first Mexican cardiologist Ignacio Chávez, made his receptional thesis on digital and from it, two fundamental concepts that are valid to date stand out; In the first place, the professor mentions that this drug is useful to treat HF, for damage systolic function (SF) "only when the heart shows signs of weakening is when it is permissible to resort to tonic medication: It is not necessary to tone up the heart that does not need tonics"[(1)]; meaning that digitalis is only useful for treating systolic dysfunction (SD). Second, he emphasized that the best therapeutic result was obtained by using lower doses than those used at that time[(1)]. Treatment of heart failure was restricted to digitalis medication associated with diuretics

After the DIG Study[(2)] published in 1997, there was a clear decrease in the use of digitalis for the treatment of heart failure (HF) has been observed; moreover, when new drugs have emerged that have proven useful in these patients, especially because they significantly reduce mortality and that is why it is a drug as old as digitalis, it is really obsolete in our time as a large number have done of cardiologists. However, to conclude this assertion, it would be worth reflecting on whether this old drug has no place in the current medical management of HF, so it is worth reviewing whether there is evidence of its usefulness when analyzing the most important studies that have been carried out throughout the 20th century to discover its therapeutic properties, which could justify its use in our time.

II - Scientific research of digital medication:

In 1961 Braunwald experimentally demonstrated the positive inotropic effect on isolated myofibrils. (Figure 1)[(3)]; later, in 1964, Dean T. Mason demonstrated how digitalis, with its inotropic effect, significantly improves cardiac output and tissue perfusion, and at the same time blocks adrenergic action, producing arteriole and venous dilatation, thereby reducing afterload and preload, which is followed by a marked clinical improvement in patients with HF quantitatively increasing blood flow, reducing peripheral resistance, as well as central venous pressure and heart rate[(4)](Figure 2); effects that are opposite when digitalis is administered to subjects who do not have HF (with normal systolic function (SF) since in them peripheral resistance increases, cardiac output and blood flow are reduced (Figure 3), facts that show that the digitalis effect is only useful in patients with HF and are counterproductive when administered to patients with normal SF[(4)], facts that corroborate the clinical observations made 40 years earlier by Professor Chávez[(1)]. This digitalis effect is demonstrated by Vatner and Braunwald in 1974 (Figure 4), by administering intravenous Ouabain to dogs with HF, the dp/dt increased very significantly, an effect that was insignificant and of very short duration in dogs with normal cardiac function, with which it also show that digitalis drugs are useful in the failing heart, but not in the normally functioning heart[(5)].

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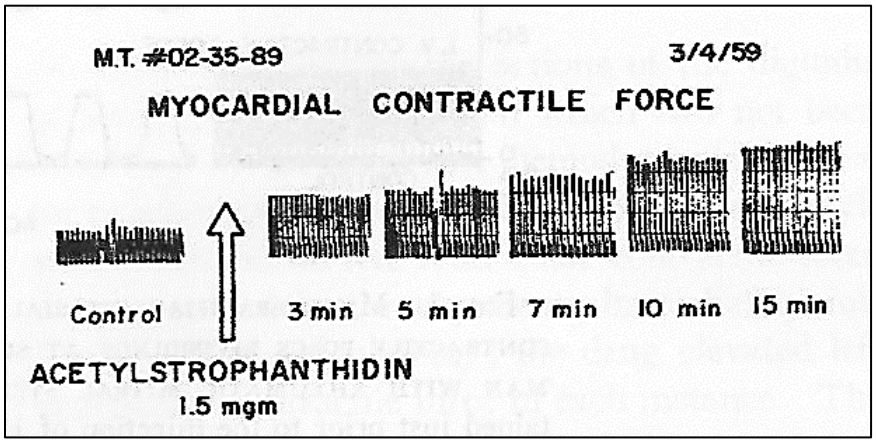

Figure 1: The contractile force increased 89% in normal myofibrils with Ouabain in relation to the basal conditions.

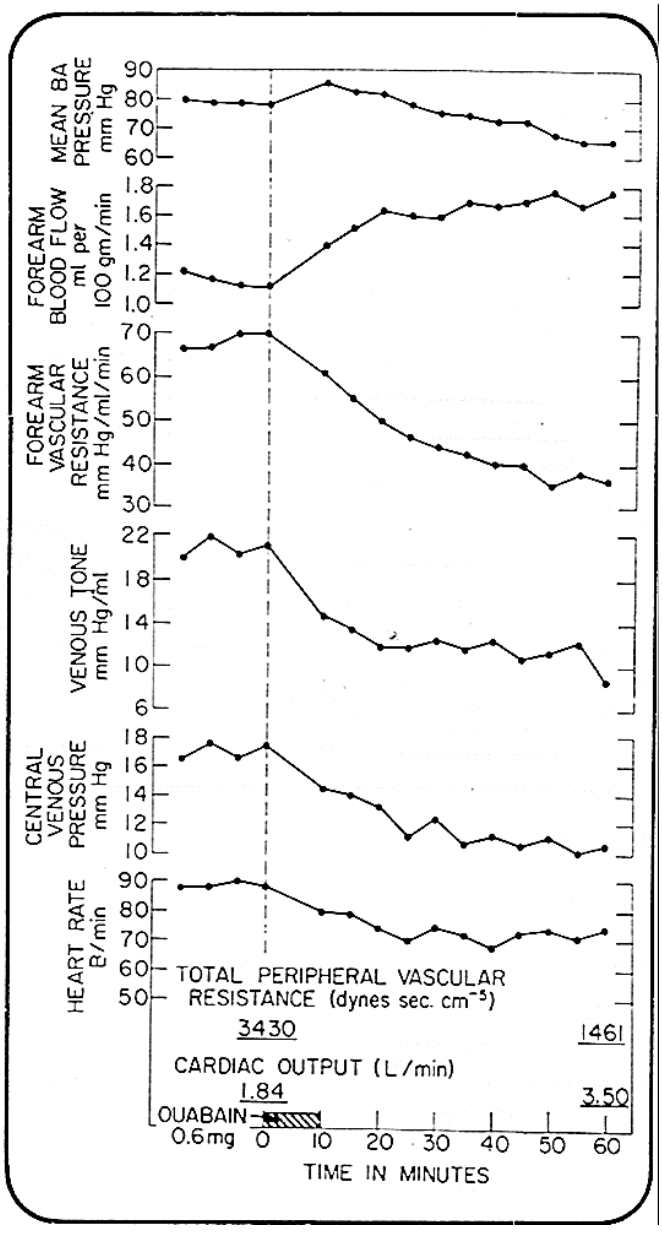

Figure 2: Peripheral Effect and cardiac output of Digitalis in Patients with Heart Failure (3)

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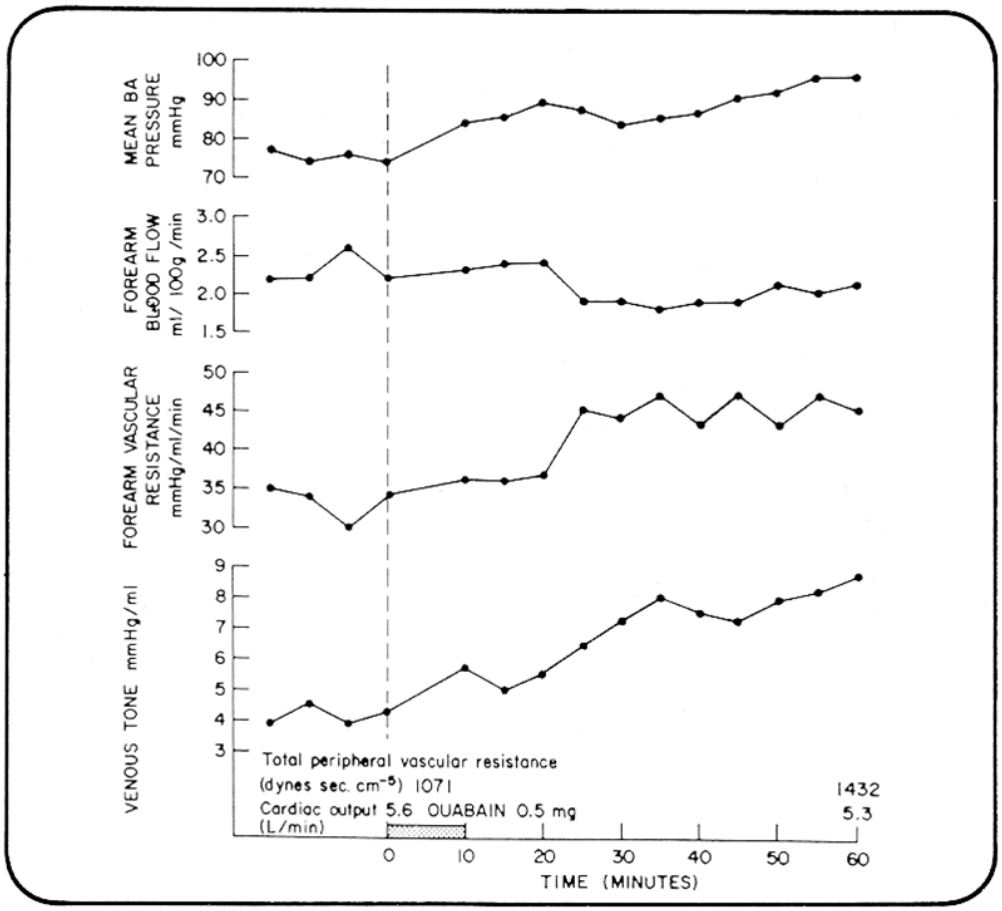

Figure 3: Digitalis in Peripheral Effect in Patients without HF

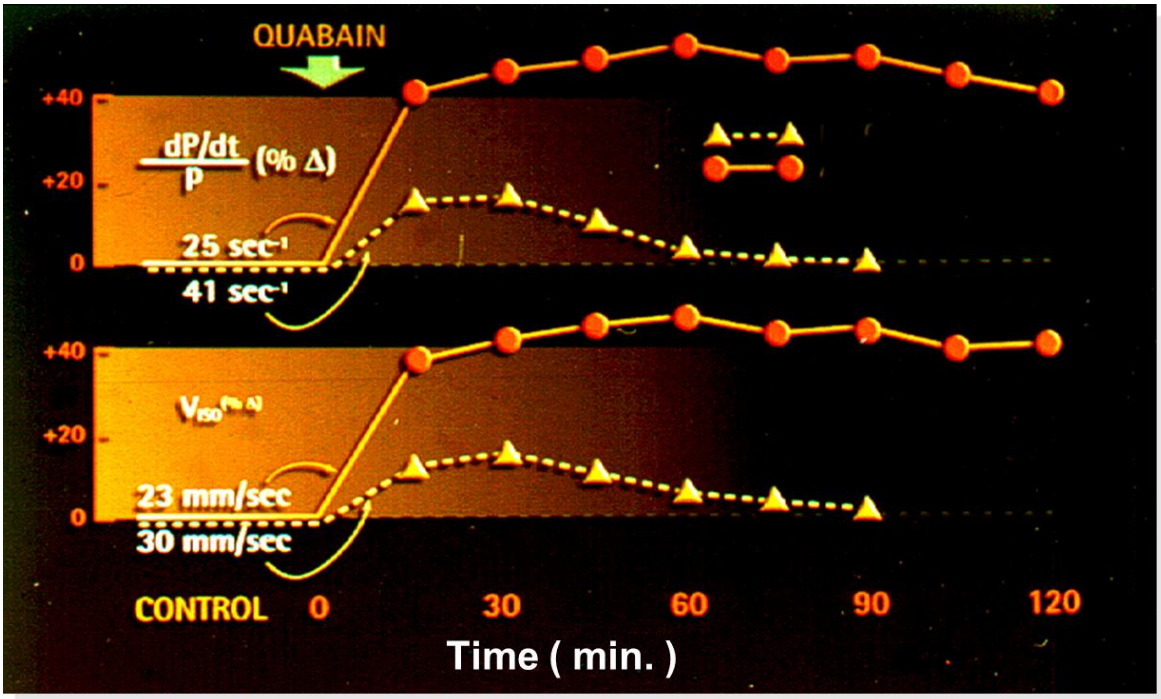

Figure 4: Effect of Ouabain on dP/dT in Normal and Failing Hearts in dogs with and whithout HF

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It is important to emphasize that digitalis is the only inotropic drug that reduces myocardial oxygen consumption (MVO_2) in HF. In a study in which it is said that increased MVO2 consumption was found in myocardial infarction, the animals studied did not have HF (without EF), so, it cannot be concluded that in these cases HF increased MVO2 was due to AMI[7], because the balance between its determinants is favorably affected: increased contractility increases MVO_2, but this effect is offset by decreased heart rate (decreases MVO_2) and wall stress (pre- and afterload) which reduces MVO_2 and the bottom line is that the inotropic effect is accompanied by a decrease in MVO_2 [6,7] (Figure 5); I emphasize that digitalis is the only inotrope that has this effect. There are various studies that ensure that digitalis has deleterious effects on myocardial infarction. But in them they study the digitalis effect in myocardial infarction and not in HF that complicates the coronary event[8-10], so it should be clarified that digitalis should not be administered in patients with AMI whose SF is normal, since in them the MVO_2[7] does increase and can increase the extension of the infarct.

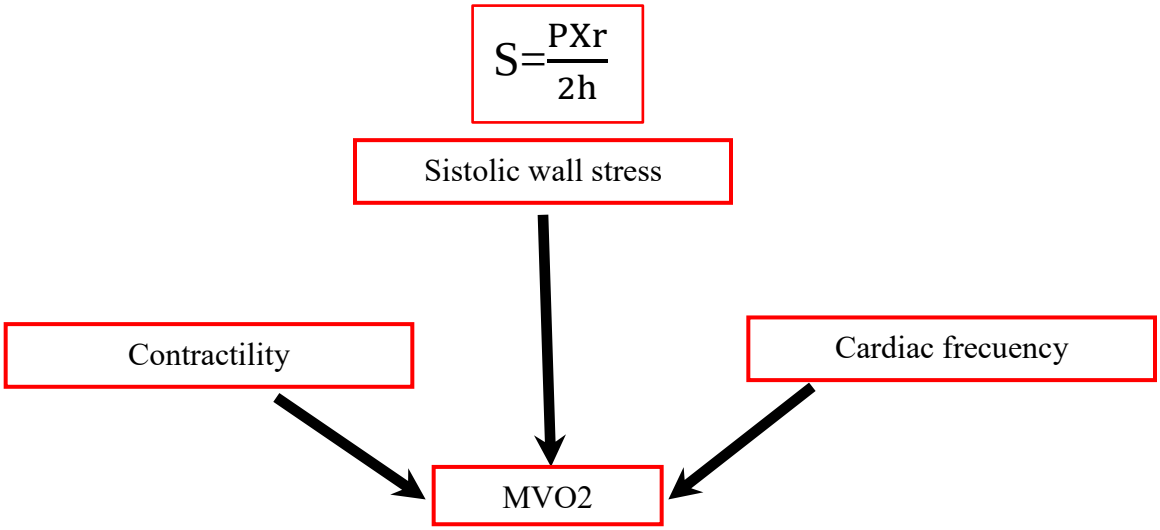

Figure 5: Determinants of Myocardial Oxygen Consumption (MVO2)

III - The first scientific study of digitalis treatment and mortality:

When looking at the DIG(1) study of 8,000 (Figure 6A) HF patients, the question arises, why were 1,000 patients who had minimally depressed SF (expulsion fraction (EF) >45%) (Figure 7) or no HF studied? when previous studies had already shown that digitalis had no effect or had an adverse effect in patients without HF(1-5), which obviously contaminates the mortality statistics when 1,000 patients have no or minimal HF, since there is evidence which shows that the mortality of this disease is directly proportional to the reduction in the EF(11-14). On the other hand, in the same DIG study, it is shown that the mortality of patients with HF is significantly reduced with digitalis by preventing relapses (Figure 6B); on the other hand in symptomatic HF(2), this fact had already been demonstrated by the PROVED and RADIANCE TRIAL, which showed that in patients who were hospitalized for symptomatic heart failure who were

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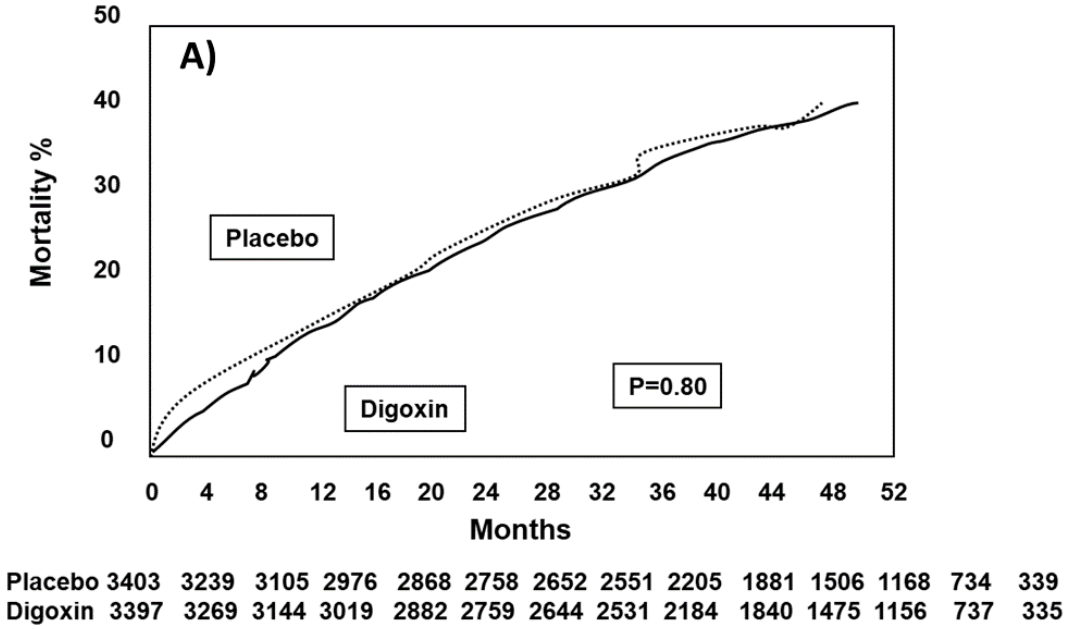
discharged asymptomatic, a group with only diuretic and placebo returned to the hospital at 3 months, 44% with symptomatic HF; another group was discharged with ACEI, diuretic and placebo and at 3 months 30% had relapsed in HF; when they were discharged with digoxin, diuretics and placebo, the relapse was 20% and finally when they were discharged with the triple regimen, only 5% of the patients relapsed, which shows that the combined therapy is superior to treatment isolated.



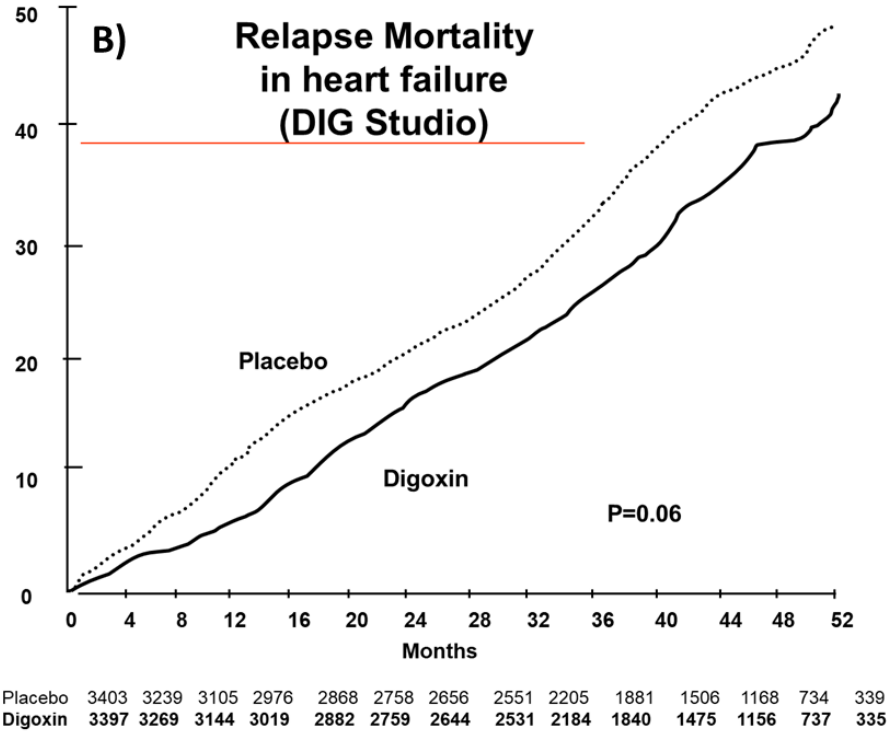


Figure 6: Effect of Digitalis on Mortality in Chronic Heart Failure

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Ancillary Trial (Left Ventricular Ejection, >0.45)

In the ancillary trial, there were no significant differences in baseline characteristics between the 492 patients assigned to digoxin and the 496 patients as signed to placebo. There were 115 deaths in the placebo group (23.4 percent) and 116 deaths in the placebo group (23.4 percent; risk ratio, 0.99; 95 percent confidence interval, 0.76 to 1.28).

Figure 7: 1000 patients with normal or slightly decreased EF (DIG)

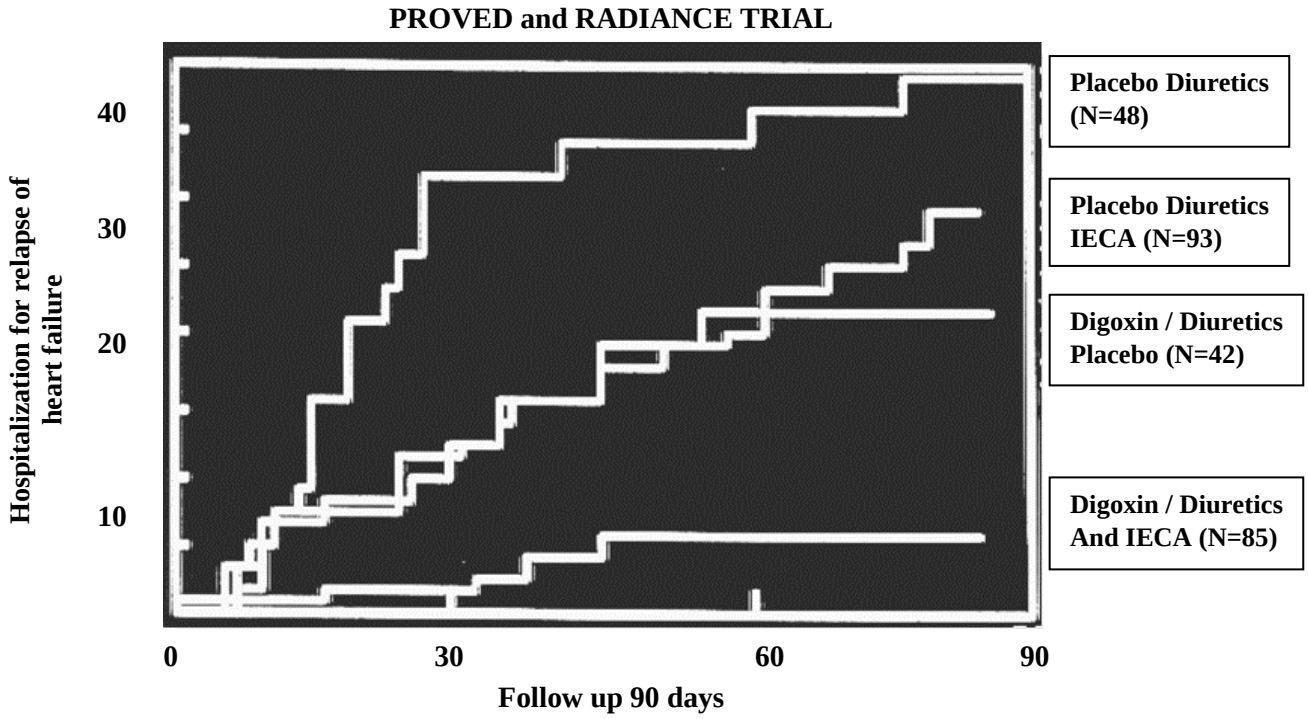

Figure 8: Digitalis in Heart Failure

IV - New studies of digitalis over other aspects of the heart function

On the other hand, it is important to mention that digitalis has a modulating effect on the neuroendocrine system, by blocking the secretion of catecholamines and renin in patients with symptomatic HF[16,17](Figure 9), as well as its vagal effect, which restores the function of the baroreceptors (Figure 10) with what that heart rate variability is recovered in these patients [17,18] which, as we know, reduces the possibility of sudden death, finally, digitalis, due to its vagal effect by reducing heart rate, restores the Bowditch effect (Figure

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11), which is lost with sinus tachycardia sustained by adrenergic activation[16,19,20]

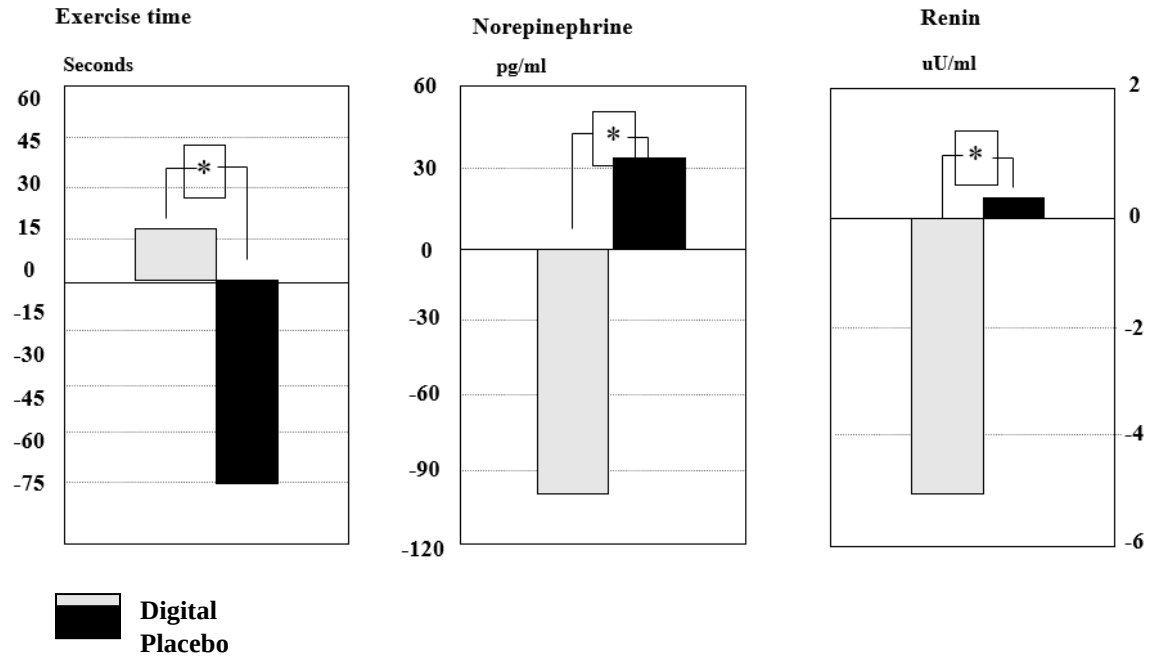

Figure 9: Digitalis Effect of Neuroendocrine System

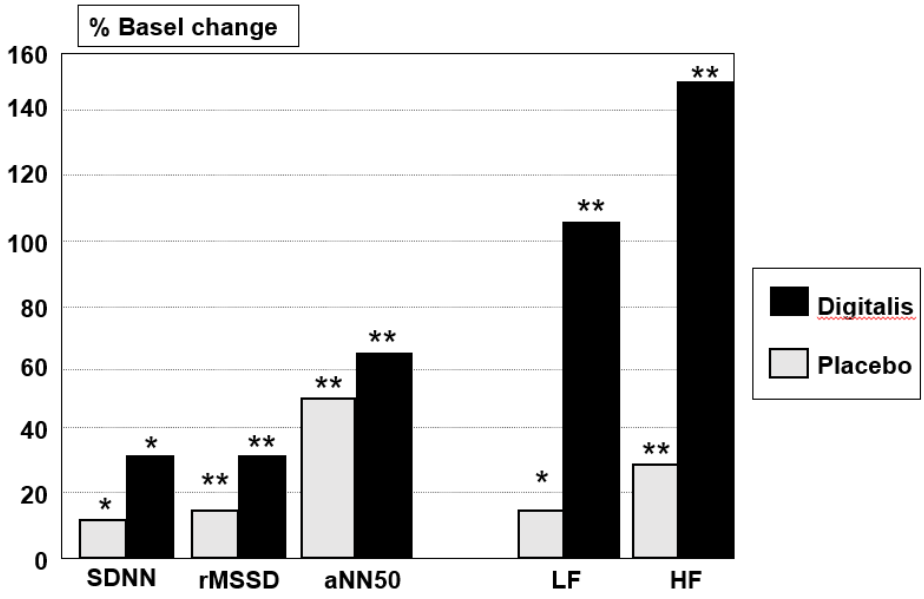

Figure 10: Digitalis Effect on Heart Rate Variability

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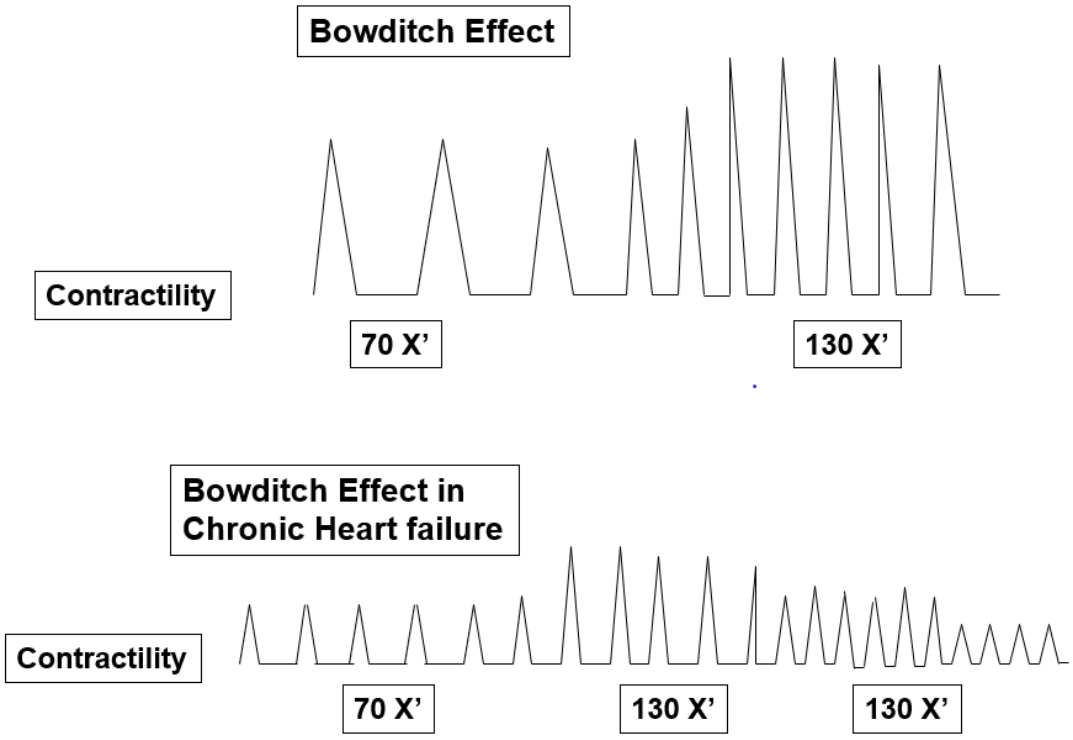

Figure 11: bowditch effect vs bowditch effect in chronic heart failure

Finally, the introduction of the name of diastolic dysfunction (DD), where SF is normal (> 50%)[21] as "HF, with preserved SF", inclusion that is due to the fact that both entities share retrograde symptoms that are very similar, but whose pathophysiology is completely different, since HF activates the neuroendocrine system, which is ultimately what leads to death in patients[22] while DD does not activate said system[23] and this explains why mortality from HF[12-14] is significantly greater than DD[21]. Even more so, even though today the concept of "diastolic heart failure" has been arbitrarily distorted, since for some, this entity is identified when the EF is > 45%[2], for others, when it is > 40% or > 35%[24,25], when in reality the normal EF is > 50%[26,27] which is what should be called "preserved systolic function"; This explains the confusion that has arisen when interpreting the meaning of BNP, since the mechanism for its secretion depends on increased stretching of the ventricular myocardium (increased diastolic stress or preload)[28] so it is to be expected that this peptide is found elevated only in patients using the Frank mechanism Starling to normalize cardiac output[28,29] and in some publications it is mentioned that in "heart failure with preserved systolic function", where preload if systolic function is normal (EF > 50%) BNP should also be normal, but as was mentioned, in the concept of "preserved systolic function" the EF is considered to be above 35%[28,29], patients with HF and others with normal SF are really mixed, which is what explains why it is elevated in the publications, "although a little less than in systolic dysfunction"[28,29] and this is due to the fact that the arbitrary definition[25,26] different from normal values, includes in the term "preserved systolic function", patients who have an abnormally reduced EF (between 35 and 45%)[25,26] that is, they are really patients with HF who do not have preserved SF, finally, the therapy that reduces mortality in patients with heart failure

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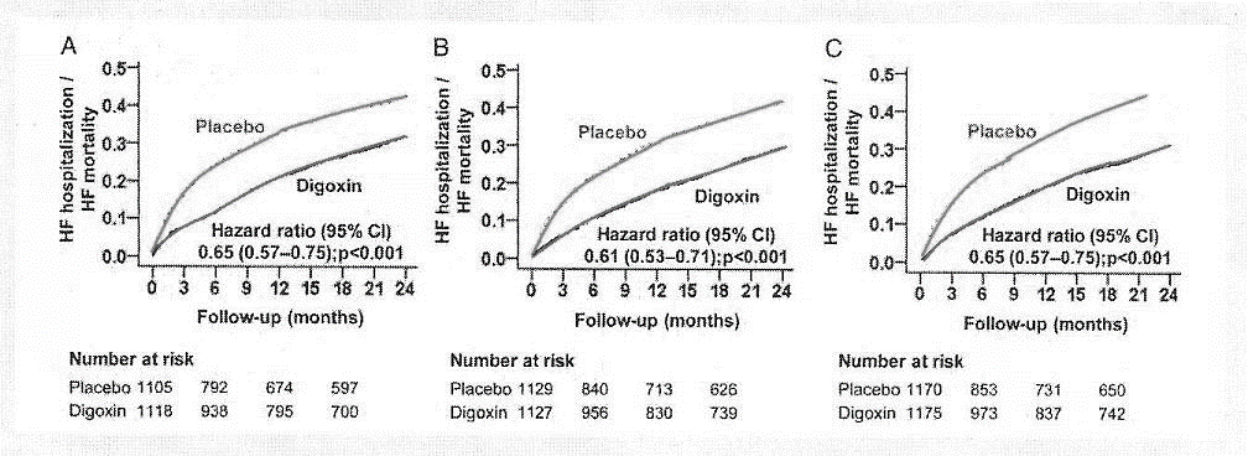
it has no effect in patients with "HF and preserved SF"[30], since the greatest determinant of HF progression is the level of EF[12,14] and in patients with SF " preserved", this effect should not be found, since in them the progression of HF and mortality is significantly lower[31]; since the neuroendocrine system is not activated in them.[23]

V- The DIG substudy in relation to mortality

When the evidence of the effects of digitalis medication is analyzed, the great value of the recently published article by Gheorghiade et al[32] can be understood in which he rescues the true value of digitalis medication when he ranks the most serious patients in the DIG[2] study: in NYHA functional class III and IV, with EF < 25% and WHR > 55% and demonstrates that the mortality of this group of patients with the highest risk at 37.9 months (Figure 12), even, Gheorghiade and Braunwald suggest that digitalis should be used in patients with acute severe heart failure, fact that we have corroborated in clinical practice showing the results of digitalis-nitroglycerin-furosemide-spironolactone and captopril treatment in this patient with a severe acute myocardial infarction (Figure 13).[33] Digitalis is significantly reduced by all causes, by hospitalization and by sudden death; on the understanding that the vast majority of these patients received ACE inhibitors and diuretics together (triple regimen)[15]. These authors also compared this high-risk group with low-risk patients (EF > 45%) and showed that the effect on mortality was not different from the group that received placebo, which shows that in the DIG study, the 1,000 patients with normal or slightly depressed cardiac function definitely influenced the final result in which there apparently was no beneficial effect of digitalis on the mortality of these patients[2]. The results of Gheorghiade study is similar to study (COPERNICUS Study)[34] (Figure 14) achieved by Carvedilol in patients with HF in functional class IV.



A) Functional class III-IV **B) EF < de 25%** **C) ITC > de 55%**

Figure 12: DIG substudy. Mortality in the most severe patients

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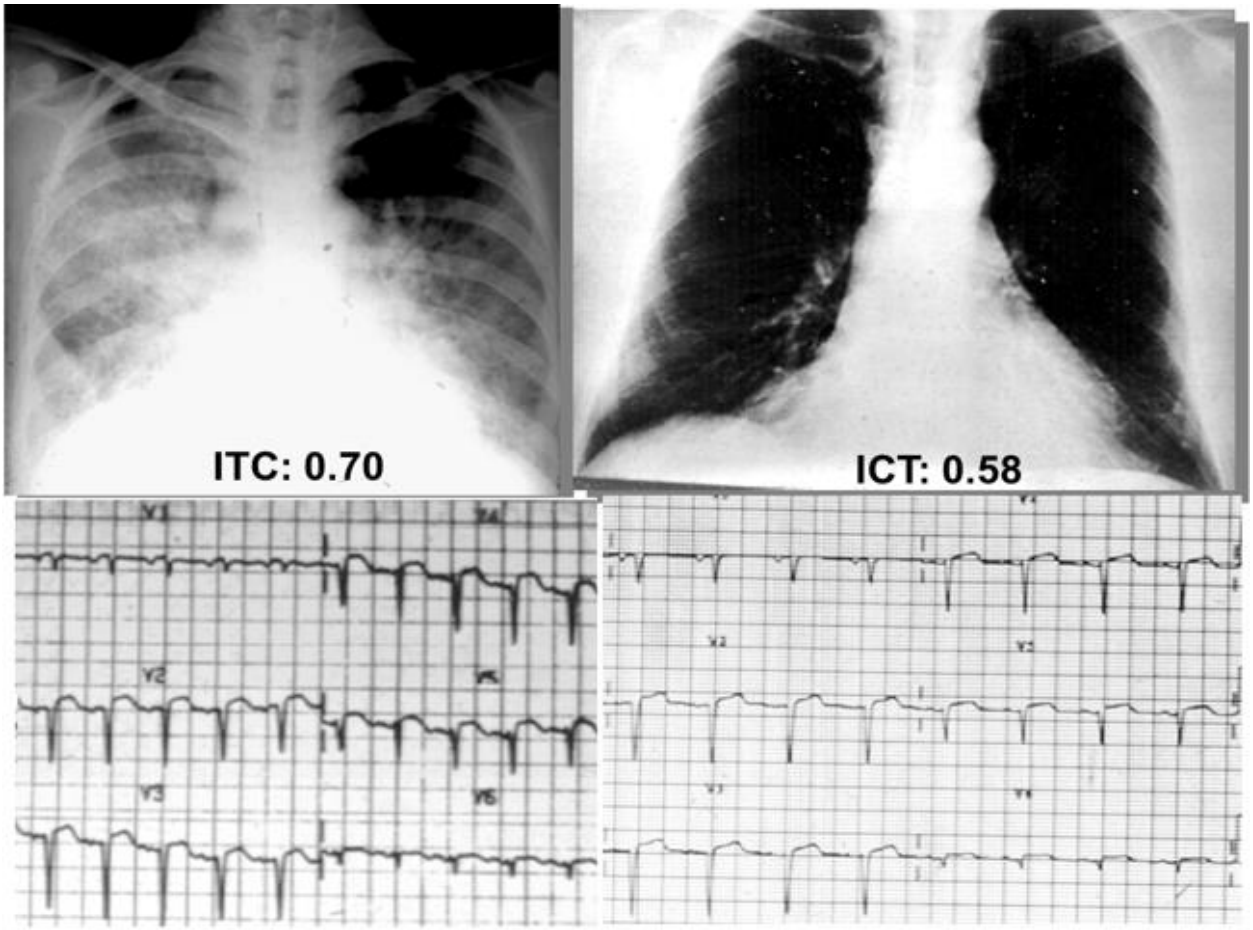

ACUTE HEART FAILURE (AHF) WITH PULMONARY EDEMA

24 hours After treatment
The patient survived this event for a further 12 years

Figure 13: Digitalis in acute heart failure (pulmonary edema)

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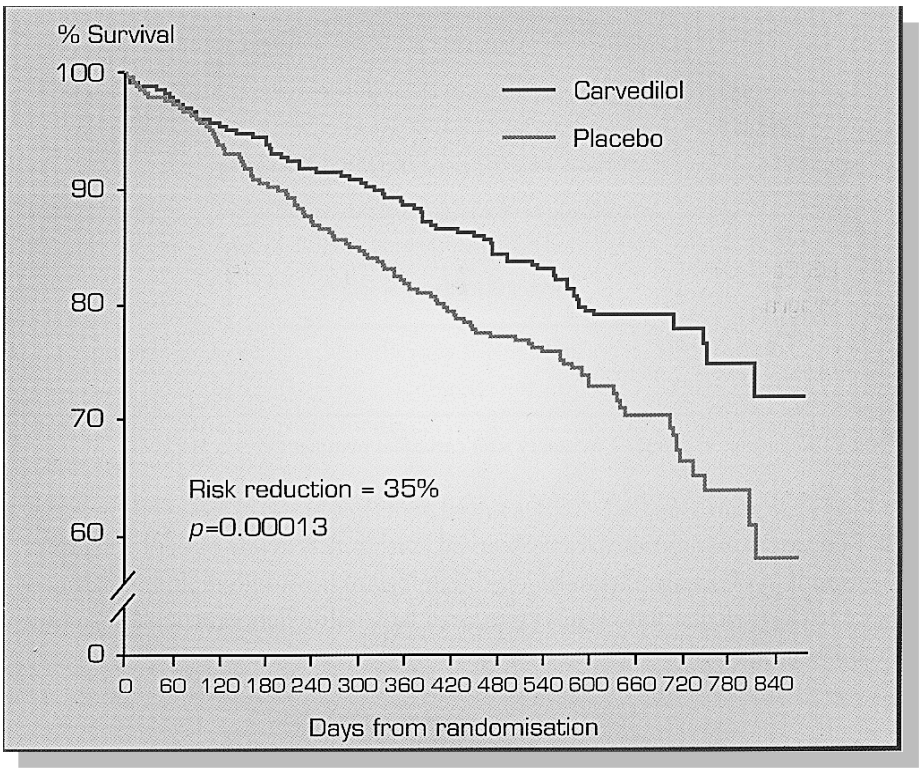

Figure 14: Carvedilol in heart failure in functional class iv (copernicus study)

Medications currently accepted for the treatment of HF (digitalis, diuretics, spironolactone, ACE inhibitors, beta-blockers) have shown their maximum usefulness in combination by adding their pharmacological benefits; each one in isolation has a significantly lower beneficial effect, but the combination between them, which must be individualized to the condition of each patient, improves functional class and reduces mortality, which is the most important objective in patients with HF.

V – Conclusions [1,3,7,11,12,16,18,22,32,33]:

The clinician and especially the cardiologist, thoroughly understands the digitalis effect in patients with and without heart failure, and all the pharmacological characteristics on inotropism, the neuroendocrine system, the autonomic nervous system, heart rate, baroreceptors, the Bowditch effect, functional class, real effect on mortality reduction, the clinician will be able to make a correct use of the digital medication of its benefits, toxic effects, its contraindications of patients with heart failure, in other words, they must be clinically prepared for correct diagnosis and the medical study of the patient (Table I).

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Table 1: Digitalis in Heart Failure

Conclusions:

1. Digitalis is the ONLY inotropic drug that REDUCES MVO_2 in patients with heart failure, including patients with acute myocardial infarction.
2. Digitalis blocks the neuroendocrine system (catecholamines and renin), like IECA and betabloquers .
3. Restores baroreceptor function and heart rate variability.
4. Restores the bowditch effect.
5. The combined therapy has better results and can be used in both acute or chronic heart failure.
6. Reduces in combined therapy mortality in patients with heart failure, especially in the most severe patients.

Can be reached on the use of digitalis in HF: it is the only inotrope that reduces MVO_2, in patients with HF, even in patients with AMI of the myocardium[6,7]; blocks the neuroendocrine system (catecholamines and renin)[16,17]; restores the function of the baroreceptors and thus the variability of the heart rate[18]; it has a beneficial Bowdtich effect in HF by suppressing sustained sinus tachycardia[18-20]; significantly reduces relapses and mortality[17,18,19,20] for this concept, in patients with more severe HF[32]; and it should not be used in patients with DD ("HF with preserved EF") [1,8-10]

a) When the clinical cardiologist takes into account the demonstrated evidence, he will be in a position to decide whether or not to use digitalis in combined therapy for HF, when it will be indicated and when it is not useful or dangerous for the patient.

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