Cardiovascular morbidity and mortality: reduction by long hemodialysis, the Tassin experience.

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Long hemodialysis (HD), 3 x 8 to 12 hours per week on 1 sq-m flat plate cuprophane dialysers, has been the empirical most achieved form of dialysis in the 70's, the "gold standard"[1]. Technical advances, changing scientific views on uremia pathophysiology [2], and economical pressure to make a better use of the scarce dialysis stations have led to the apparition and wide expansion of "short" dialysis [3]. In Tassin the 8-hour hemodialysis (HD) has remained the unique treatment method for almost all patients whether in the unit or at home since 1968. After more than three decades of follow-up, the overall results of the empirical long slow HD representing more than 6500 patient-years of experience are worth reviewing.

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- The session
8 hrs x 3/wk, cellulosic membrane
Kt/V (Daugirdas II)= 2.0 (0.41) PCR= 1.2 (0.3)

- Between the sessions
Intake: 1.2 g/kg Protein BW/day
31 Kgcal/kg/d
5 g ClNa/d
Mean Interdialytic weight gain: 1.6 kg
No antihypertensive in 95% pts > 2 HD months

Tassin experience summary

Three sessions of seven to eight hours per week are performed overnight during the sleep or in the day time according to patient's possibility and preference. Home dialysis has been used in a large portion of the population up to the 80's (at which time 50% of the patients dialyzed at home). Then, multiplication of dialysis units, transplantation rate increase and patients case-mix worsening have lad to a steady decrease of the proportion of patients treated at home. Only 10% of Tassin patients are treated at home presently.

Until 1995 we used a poorly "biocompatible" setting including cuprophane® membrane, acetate buffer and plain softened water. Since 1996 bicarbonate buffer has progressively been substituted to acetate. Since 1998 low-flux polysulfone dialyzers have progressively replaced cellulosic ones. Finally in January 2001 a complete change occurred in the water treatment. It uses now a reverse osmosis treatment completed by an ultrafiltration system. Moderate (220 ml/min) blood flow has been used throughout the experience.

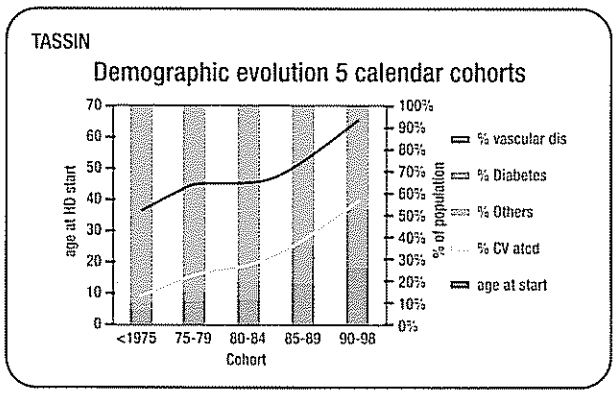
Since 1991 a "short" HD program has been set up as a complement of the long HD. It uses a 3x5 or 6h schedule with large area size dialyzers (1.7 to 2.5 sq-meter), and 300ml/min blood flow. This shortened schedule is presently used in 25% of Tassin patients.

Whatever the dialysis session duration the dose provided is large: the mean delivered urea Kt/V using second generation Daugirdas method [4] is 2.0 per session, 6.0 per week [5]. The mean normalized protein catabolic rate is over 1.2. The mean protein and calories intake are 1.2 g/kg and 32 kgcal/kg/day respectively. The patients are requested to maintain a low salt diet. No salt is added to the food and processed food is avoided. Accordingly, the average sodium chloride intake is 5 to 6 g per day. On the other hand the patients are not requested to restrain from drinking. Using a reasonable (138 mmol/L) dialysate sodium, the mean interdialytic weight gain is 1.7 kg (2.5% of mean dry weight).

All antihypertensive medications are stopped in over

95% patients within the two first months of HD. It is a crucial point of the method that during the initial few weeks of dialysis the antihypertensive treatment is tappered down and stopped in each and every patient in conjunction with the lowering of his extracellular volume to achieve "dry weight" and normotension [6].

As in many units worldwide Tassin incident population profile has changed drastically over calendar years. The mean age at start increased from 36 years in 1968 to 66 in 1999. During the same period diabetes mellitus and nephrosclerosis prevalence in the incident population crept up from 5 to 53% and the proportion of patients with cardiovascular comorbidity (myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, and peripheral vascular disease) increased from 6 to 61% of incident patients.



Mortality data

Due to the increase in risk factors, the crude mortality expressed as a Kaplan-Meier survival curve [7] has steadily increased along calendar years. The mean half-life of the cohort of patients starting HD between 1968 and 1975 wes 17.5 years, it dropped to only 5 years for the most recent cohort (starting HD after 1992) [5]. But this compares patients almost free of comorbid conditions (first cohort) to aged sick patients with heavy comorbid conditions (last cohort). A realistic view of the mortality evolution in a given unit must take into account the changing demographic and comorbid patterns of the population.

To achieve this correction, the patients' risk level must be stratified according to identifiable patients risk factors. The Standardized Mortality Ratio (SMR) adjusts for age, race, sex and cause of renal feilure using the United States Renal Data System (USRDS) standard mortality table as the reference [8]. For each calendar year the ratio between observed and expected deaths numbers according to the standard table is calculated. A SMR value inferior to one translates a better than expected survival. The average observed mortality in Tassin is 0.45 of the expected value according to US standards for grossly similar patients. It has remained fairly stable around this value over the last 12 calendar years (Table 1) in spite of the worsening case-mix.

Table 1

Standardized mortality ratio (SMR) Tassin 1989-2000

Calendar year	O/E death†	SMR	P value
1989	24143.7	0.53	< 0.005
1990	14/42.4	0.33	< 0.001
1991	18/44.7	0.40	< 0.001
1992	15/46.1	0.33	< 0.001
1993	23/47.7	0.48	< 0.001
1994	20/50.3	0.40	< 0.001
1995	23/57	0.40	< 0.001
1996	27/56.4	0.51	< 0.001
1997	25/48.5	0.52	< 0.001
1998	26/47.6	0.55	< 0.005
1999	27/67.5	0.41	< 0.001
2000	31/69.9	0.44	< 0.001

†O/E: observed / expected number

Comparing Tassin mortality to the only available long-term French series of 4-5hr hemodialysis reported by Degoulet et al. several years ago [9] shows that long HD mortality wes lower (52.4 vs. 99 deaths per 1000 pt-yrs. p<O.001). There was no difference in several specific (infection, cancer, or others) causes of mortality between the two series but for the cardiovascular mortality which was much lower on long than on short HD (19.8 vs. 44.6 cardiovascular deaths per 1000 pt-yrs, p<O.001).

We splitted Tassin long dialysis population in 2 cohorts (equal in number) according to integrated predialysis mean arterial pressure (MAP) calculated over the whole dialysis treatment time, and then we analyzed their respective Kaplan-Meier survival. The subgroup of patients with the lowest MAP (n=382 pts; mean predialysis MAP=89 mm Hg) had a significantly lower mortality (p=0.003) than the subgroup with a slightly more elevated MAP (n=383 pts; mean predialysis MAP=103 mm Hg). The difference in survival was mainly explained by a lower cardiovascular mortality in the lower MAP subgroup, 12.7 vs. 28.1 cardiovascular deaths per 1000 pt-yrs (p<0.01).

The Cox proportional hazard model [10] analyzing the

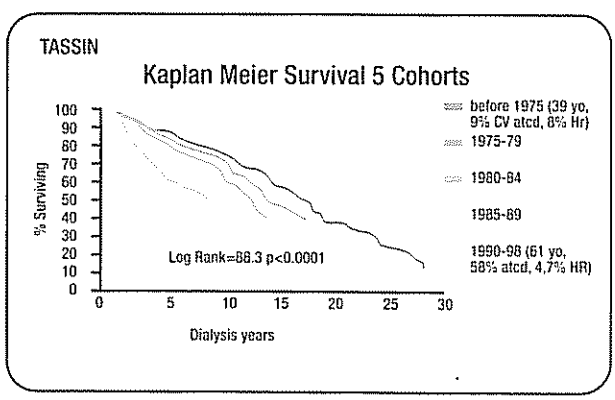


Table 2

Proportional Hazard Cox model of mortality of 786 patients

	Regression coefficient	95% Confidence interva	Relative risk	95%Confidence interval
Ageat start	0,049	(0.033, 0,067)	1,050	(1.033, 1.069)
Diabetes	0,606	(0.131, 1.081)	1,833	(1 139, 2.947)
CV(1) antecedent	O,631	(0.204, 1.057)	1,879	(1.226, 2.878)
MM(2) indox-0,404	(-0.681, -0.128)	0,668	(0.506, 0.880)	
KW urca	0,153	(-0.348, 0.675)	1,165	(0.706, 1.964)
Mean MAP(3)	O,033	(0.011, 0.056)	1,034	(1.011, 1.057)
Serum Albumin	-0,029	(-0.064, 0.007)	0,971	(0 938, 0.993)

(1): CV= Cardiovascular antecedent (Myocardial infarction, angina, cerebrovascular accident, transient ischamic attack, peripheral iscemia)
(2): MM= Middie Molecuie
(3): MAP= Mean Arterial PressUre

same patients survival shows (Table 2) that age, cause of renal feilure and cardiovascular antecedents are very powerful predictors of mortality. These factors are not amenable to medical action as treatment-related factors. Among treatment-related factors urea Kt/V is not a significant predictor of survival. At opposite, the more time-dependent middle molecule index calculated using Babb's method based on vitamine B12 clearance [11] is significantly correlated to survival (the higher the middle molecule removal rate, the longer the survival)[12]. This interesting feature has been confirmed recently in a subset of the USRDS popUlation [13]. But the strongest predictors of mortality are serum albumin and even more predialysis MAP. For each 10 mm Hg increment of the predialysis MAP the risk of death increases by 34%.

So, a long HD allows for a long survival. This long survival is mainly due to a low cardiovascular mortality. The main feature of long HD which could explain this result is the good blood pressure control.

Is BP control really good in long slow hemodialysis?

The mean observed casual predialysis BP calculated from all values of each patient (128/79 mm Hg) is within the normal range advised by the VIth Joint National Committee on BP [14]. Besides, ambulatory BP monitoring values are also within normal range at least for daytime (121/72 mm Hg) and circadian values (119/71 mm Hg). However the night time values (118/67 mm Hg) are slightly more elevated than normal (106/64 mm Hg) due to the lack of nocturnal dip in 50% of the patients.

One cannot exclude some "center effect" in the achieved results. But all units where a long dialysis was in use in the 60's [15-18] as those where it is still in use today [19-22] report the same excellent patients survival and low

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Standarized mortality ratio 1989-2000

Calendar Year	O/E deaths *	SMR	p. value
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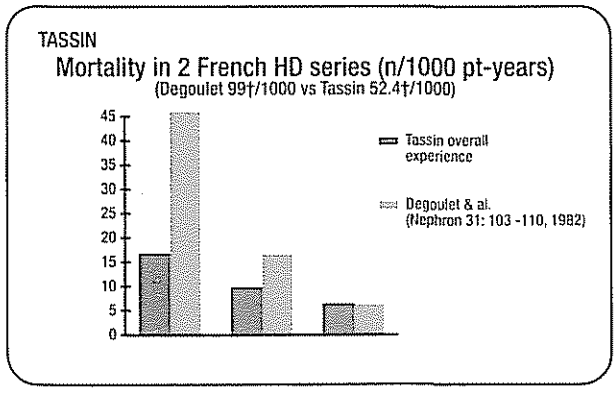
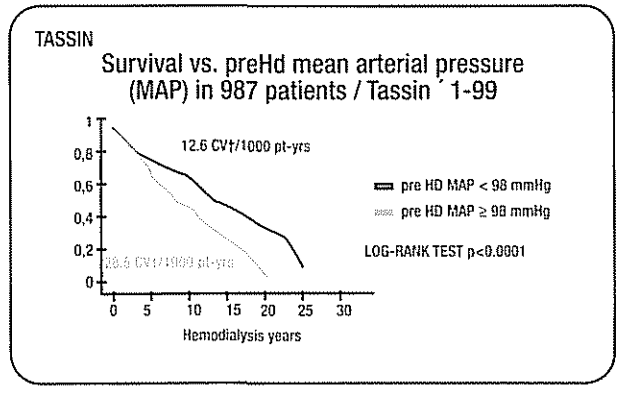
* Observed / expected





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- A long HD allows for a long survival.
- This long survival is mainly due to a low rate of CV mortality
- The main feature of long HD which could explain this is BP control

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IS BP CONTROL REALLY GOOD IN LONG HD?

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Mean predialysis BP values in all 970 long HD pts. (antiHT therapy in <5% of pts after 3 months HD)

- Mean casual pre dialysis BP=128/79 mmHg
  MAP=96 mmHg

Advised normal BP= 120-129/80-84 mmHg
(VI th Joint National Commitee BP)

- ABPM

	Circadian	Daytime	Nighttime
Tassin*	119/71	121/72	116/67
Staessen	118/72	123/76	106/64

*(Chazot & al. Am J Cardiol 1991; 67-723)

morbidity, as well as the same BP control without need for antihypertensive medications. The long dialysis method per se obviously allows for an excellent control of volume and of blood pressure, as well as satisfactory control of nutrition, correction of anemia, and good control of serum phosphate level. The effect of this serum phosphate control on HD patients survival has been confirmed by several groups after the initial report by Block and al. [23].

How and why does a longer dialysis improve BP control?

Normotension can be reached in long HD by achieving a normal ECV, in other words, "dry weight". This implies a low salt diet to avoid excessive interdialytic weight gain, a reasonable dialysate sodium (about 138 mmol/l) to achieve a nil diffusive sodium balance, and a sufficient ultrafiltration . This is the most powerful tool we have at hand but it is aiso the weakest one because it is limited by the patient refilling capacity, therefore by time.

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- Long HD yesterday: 90% normotensive pts on HD in the early 70's without antiHT
- Long HD today: Manchester, Glasgow, Leeds (UK), Christchurch (NZ)
- Daily dialysis short (Buoncristiani, Koistra, Lockridge, Traeger...) or long (Pierratos, Lindsay)

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How and Why does a long HD improve BP control?

Due to the intermittent nature of HD the patient oscillates between a "wet (saline overloaded) state" just before, and a "dry" (saline depleted) state just after the session. During the few hours of HD the plasma compartment is ultrafiltered down to a nadir. Refilling from interstitial space lags some hours behind. At the very end of the session the patient is hypovolemic. He returns to normovolemia a few hours later when refilling is completed. The hill-and-valley unphysiologic rhythm of intermittent HD is a critical issue which leads to conditions favoring alternatively hypertension and hypotension.

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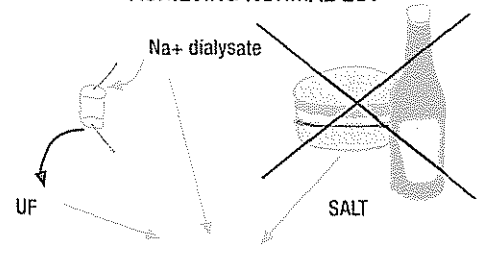
ACHIEVING NORMAL ECV



Long slow HD not only reduces hypertension but also hypotension episodes. Hypotensive episodes prevalence is less in long than in short HD. This appears in our own unit when comparing 8 hour (7% of hypotension episodes) to 5 hour (13% hypotensive episodes) sessions, but even more in units using shorter sessions (20% or more hypotensive episodes).The reduction of both hypertension and hypotension by a longer (or probably more frequent) session has a

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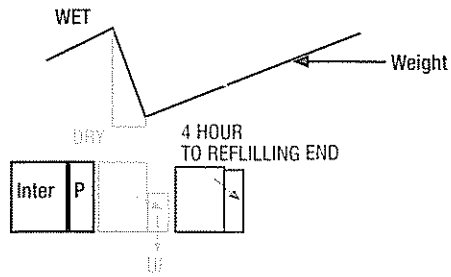
Intermittent nature of HD, ECV & weight



sound logic.

When session time decreases, ultrafiltration rate needs to be increased and hypotension gets more common. This has different effects:

-The patient has a poor perception and acceptance of the dialysis sessions troubled by hypotensive episodes or cramps and he asks for shorter sessions;

-The nurse has to cut down the ultrafiltration rate and /or to give saline infusions so that prescribed dry weight is not achieved, and the patient ends up saline overloaded.

-The physician himself, abused by the frequent intradialytic events, wrongly reevaluates dry weight. Often he also increases the dialysate sodium to alleviate cramps and hypotensive episodes. This in turn reduces the diffusive loss of sodium and leads to increased osmolality, thirst, and interdialytic weight gain.

Altogether the patient does not get to dry weight but is saline overloaded and more hypertensive, he needs more ultrafiltration, the vicious cycle is closed.

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Incidents per 100 dialysis as a function of session duration (370000 sessions)

	Diaphane	Bergamo	Tassin	Tassin
HD Hours	4,3	4	8	5
Hypotension	20,8	21,8	7,0	12,9
Cramps	10,2	11,0	2,1	2,0
Vomiting	4,4	4,5	0,6	0,5
Headache	3,0	?	0,7	1,2

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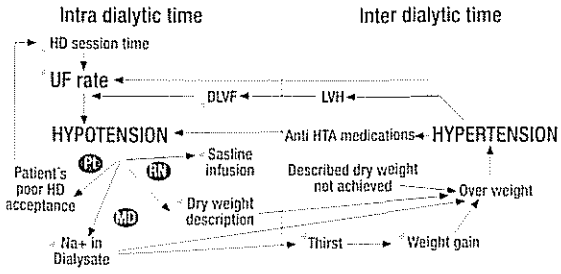
Shorter D: the Blood Presure Issue



Hypertension also aggravates left ventricular hypertrophy and decreases left ventricular function. This reduces the capacity of the heart to adapt its output to the acute changes in volume. Eventually antihypertensive drugs are added, which potentiate further hypotension during ultrafiltration. Altogether interdialytic hypertension and intradialytic hypotension keep on amplifying each other. Hemodialysis duration reduction behaves as an amplifier of BP variability.

Does hypertension impact on mortality in hemodialysis?

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YES!

- Most reports show a clear-cut relation HT/mortality

- Eliahou et al., Isr JM Sc 1977; 13:33
- Haire et al., Cardiovasc Med 1978; 3: 1163
- Vincenti et al., Am J Med 1980; 63: 363
- Rostand et al., Kidney Int 1982; 22: 304
- Degoulet et al., Nephron 1982; 31: 103
- Ritz et al., NDT 1987; 2: 293
- Charra et al. Kidney Int 1992; 41: 1029
- Tomita et al., Am JKD 1995; 25: 405
- Mazzuchi et al., Kidney Int 2000, 58: 2147

The question sound curious given Framingham and many other studies evidence in non-uremic patients, and the natural answer is yes, hypertension increases mortality. In the dialysis setting many studies have shown that mortality decreases with control of hypertension [9, 24-29]. According to these studies hypertension is very common in dialysis, it is a risk factor for stroke, coronary disease, left ventricular hypertrophy and congestive heart failure. And it is of note that mortality associated with hypertension is a long-term effect (≥10 years) in non uremic [30] as in hemodialysis patients [28, 29, 31]

On the other hand, according to others studies the relationship between hypertension and mortality is not established [32-37]. Furthermore, according to several of them, it is hypotension and not hypertension which is related to mortality. What do we know about hypotension on dialysis? First hypotension (excluding the hypotensive episodes during the session) is not very common in HD. Second, it is a marker of poor clinical condition, especially congesti-

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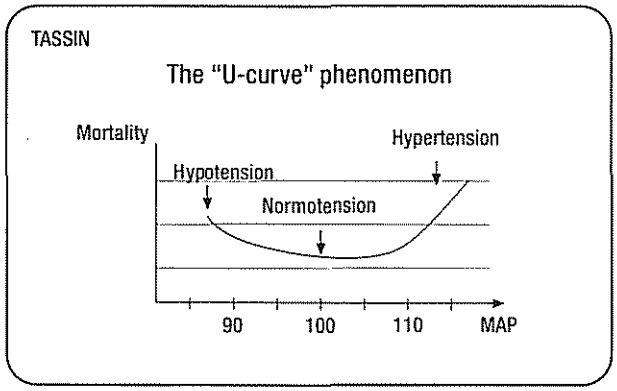
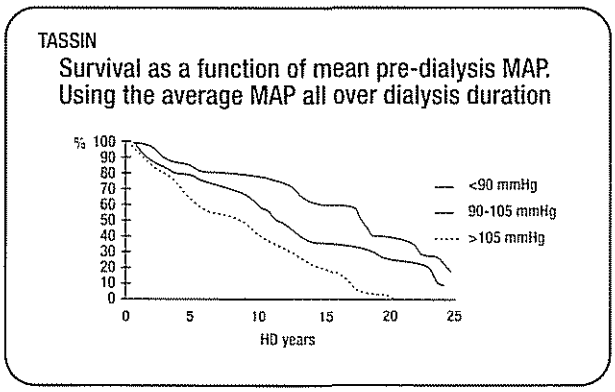
Hypertension in Gialysis Patients

- HT is very common in HD
- Low BP is a maker of poor clinical condition (CHF, frailty)
- Low BP correlates with increased coronary risk (causal relation not established)
- Mortality associated with hypotension is mostly short-term

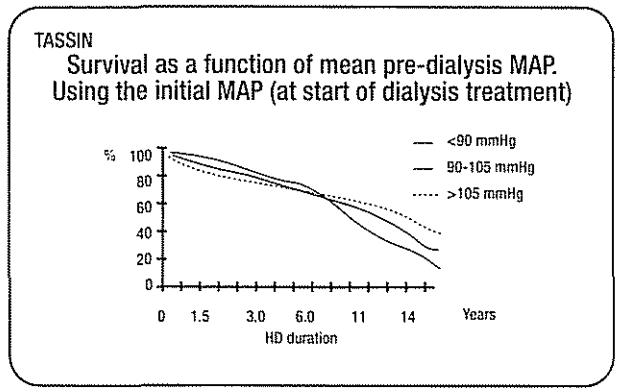
ve heart feilure or frailty. Third, a low BP, especially diastolic, may be -as for non-uremic patients- a coronary risk factor but causal relationship is not establisded. Fourth and last, the mortality associated with hypotension is mostly short-term (some months or some years).
Which is the killer? hypertension or hypotension?



Altogether if we plot mortality against mean arterial pressure, the lowest mortality correlates with normotension. Mortality is higher in hypertension, but also in hypotension. In fact this "U curve" pattern is misleading, more an intellectual construction than a reality: -First because we artificially display on the same curve all mortality whether short- (hypotension) or long-term (hypertension); -Second because different studies use different BP estimates to correlate with mortality. This second point can be illustrated using our own population data. If we observe the Tassin



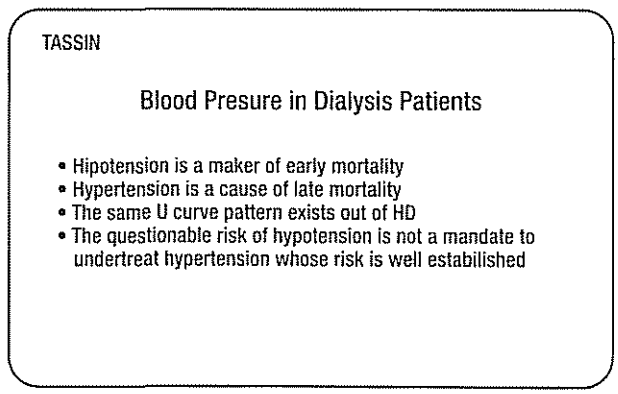
Kaplan-Meier mortality curve as a function of BP in 3 subgroups of patients according to their "integrated" mean predialysis MAP (i.e. calculated all over their maintenance dialysis time), the lowest BP subgroup has the best survival, the highest BP subgroup has the worst survival, the intermediate BP subgroup has an intermediate survival. But if we take for the same patients the value of BP at start of dialysis as the predictor of mortality, we come out with an inverse correlation. The patients with a low initial MAP have the highest mortality, the patients with the highest initial MAP have the lowest mortality, and the intermediate initial MAP subgroup has an intermediate mortality. It is of note that after 5-6 years of follow-up this relationship inverses. One must also point at the fact that at start of HD when 90% of patients are usually hypertensive, a low or even normal BP is (out of the few cases of patients with

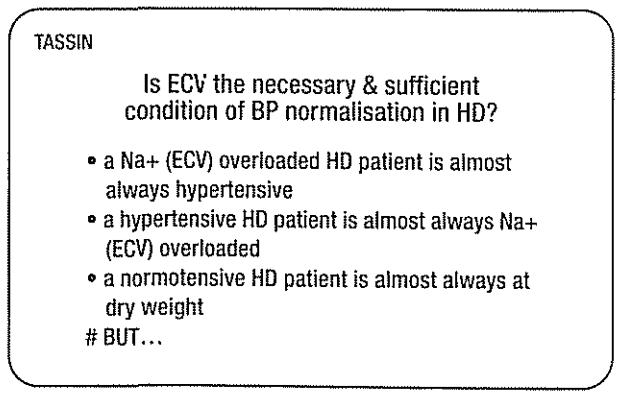


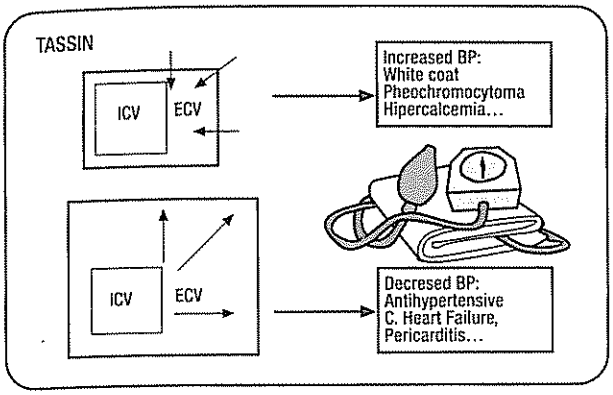
chronic renal failure behaving as "salt loosers") a marker of severe heart disease or frailty which correlate with early mortality. Mazucchi from Uruguay made the same observation in a recently published paper [29].

So altogether hypotension is a marker of short-term mortality, hypertension is a cause of long-term mortality. The same "U curve" pattern we observe has been described long ago in non uremic patients. Anyway the questionable risk induced by hypotension is not a mandate to undertreat hypertension whose risk is well established.

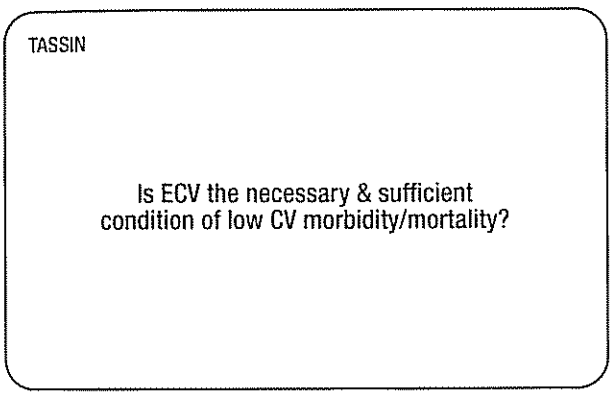
Is ECV control the necessary and sufficient condition of BP controi in HD?



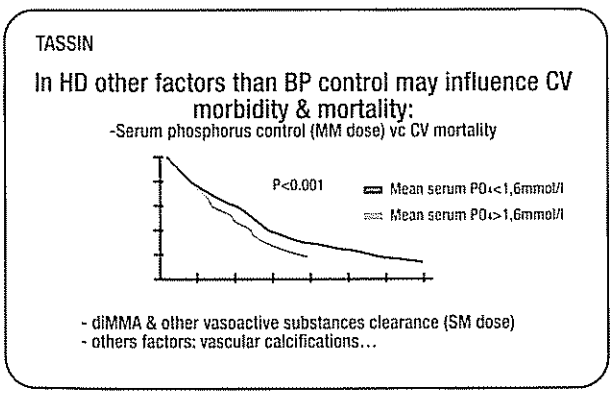




A normal BP is a mandatory condition to assert that dry weight has been achieved. As a matter of fact, a sodium (or ECV) overloaded patient is almost always hypertensive, a hypertensive HD patient is almost always sodium (or ECV) overloaded, and a normotensive HD patient is almost

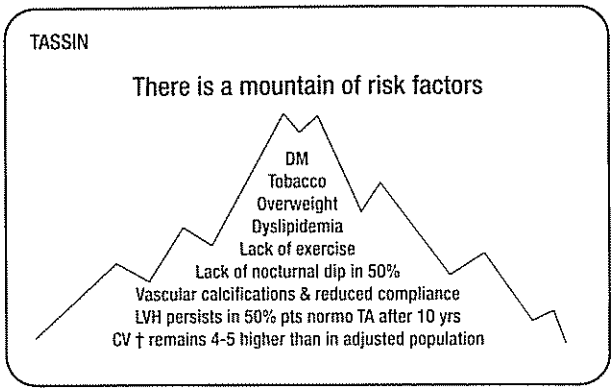


always at dry weight. But a reduced or normal ECV can coexist with an increased BP (white coat effect,



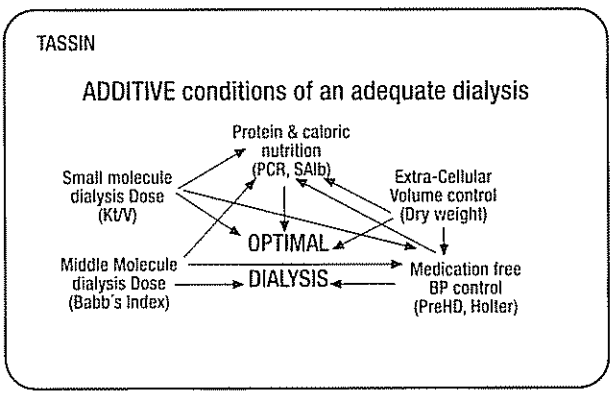
renovascular HTA, pheochromocytoma, hypercalcemia...), and on the other hand an increased ECV can coexist with a normal or decreased BP (antihypertensive treatment, congestive heart failure etc.).

So, Volume excess is by far the first determinant of hypertension in dialysis but other factors do exist that must be kept in mind.



Is BP control the necessary and sufficient condition of a low cardiovascular morbidity and mortality on HD?

Here the answer is, of course, no. For instance as suggested recently by Block [23] a high serum phosphate and/or CaxP04 product is correlated with a high cardiovascular mortality on HD. We compared the cardiovascular mortality in two Tassin subgroups of patients adjusted for age, diabetes, cardiovascular comorbidity and blood pressure. Cardiovascular mortality is significantly lower ($p<0.01$) in the subgroup of patients whose predialysis



serum phosphate is normal (>1.60 mmol/l before dialysis) than in those where it exceeds 1.6 mmol per liter.

Many other factors do affect cardiovascular morbidity and mortality. Some are linked to the treatment, others to the patient, his life style, his disease, or his comorbidity. These factors probably explein why cardiovascular problems continue to plaque long HD patients in spite of their good BP control. Among them lack of nocturnal dip, vascular calcifications, and left ventricular hypertrophy probably explain why although lower than in standard HD, the cardiovascular mortality in Tassin remains much (4 times) higher than in a standard French adjusted non uramic population.

To make a long story short, we have used Tassin data to focus on cardiovascular morbidity and mortality factors, and the way dialysis can modify them. The data show that BP extremes can be reasonably well controlled in almost all patients by increasing the dialysis session time (or alter-

natively by increasing the frcquency al' sessions?). This allows 1'01' a reduced cardiovascular morbidity and morrality, But the resuft is not perfecto the normal nyctcmeral rhythm al' BP is not restorcd in hall' 01' the patients. left ventricular hypertrophy pcrsists also in ubout hall' 01' the paticms, vascular culcifications are common.

But al' course a rcally "optimnl" dialysis nccds othcr conditions. Out of the ECV and BP control on which wc [ocused. it nccds small and rniddle moleculc large clearnnces. adcquate nutriticn. und probably severa! other conditions. Each 01' thcsc conditions is mandatory. Any 01' thern ir not Iulfilled muy sufflcc lo wrcck thc wholc ship.

Ncverthclcsst we must keep in mind that evcrywhere including in Tassin tbe cardiovascular mortality remains by lar the Iirst cause 01' dcath. thc one we must control first. lt is on this that we rnust plan uny prospcctive policy aiming ut a bcucr clinical outcorne.

Comment Vigo (B Charra)

AlI Ill1Y thanks lo Carlos GOMEZ-ALAMILLO and the organizing commiucc Ior giving us a chance lo uuend this cxciting meeting with you. 1shall use the Tassin data on Sh HD to discuss the CV morbiditv & mortality on HD.

Thc sume unchanged 3X8hr HD has been used sincc over the last 35 yrs. It providcs a Kt/V 01' about 2 per sessien. 6 pcr wcek. und a normalized PCR 01'about 1.2. Thc mean protein and calories intakes are largo, but the sodium intake is rcstricted. The mean intake is 5g sodiurn chloride per day.Thc mean interdialytic wcight gain is less than 2 kg. An cssential fcuture is that no until-IT mcdicution is uscd in 95% 01' pts after the 2nd month of dialysis. AntiHT drugs are systematically wilhdrawn in each ami every pt al start 01' dialysis.

If the treatment has relllained the same. the population ol' pts has changed a lot along years as everywherc clsc. 1 splitted here our populalion in 5 calendar cahons fralll 1968 lo 1999: DM Iyellow) and nephrosclerosis Ibluel have become increasingly common.The mcan uge at start (reel)& proportion 01' pts with CV cOlllorbidity (grsell) increased steaply. Due to the increasing risk faclors lhe crude mortulity has increased along years

As shown by lhe KM survival curves ofthese 5 cohorts crude 1110rtalily becomes worse and worse. This is the 1st and this is the last cohort curve with mean hall' life of 17 and 5 yrs respectively. But 01' course we are comparing oranges and bananas young fit pts almosl free 01' comorbidity here (sho\\') ami aged. sick pts with a heavy comorbidity there A fair outcomc unalysis must takc into accoullt lhe changc in case-mix by stratiliying the pts into risk groups as done with the Standardizecl rvlortalily Ratio (SMR) shown now.

SMR adjusting 1'01' age. race ancl cause 01' renal faillre uses the slandard USRDS mortalily tablc to calculate one yr after lhe other lhe ratio between lhe observecl and the expccted nllmber of cleaths. It relllainecl stable all along the lasl 12 years in spite ofthe change in case mix. around hall' 01' the expected number al' deaths.

If we compare Tassin mortality to lhe only availablc (vcry old) long term French series on 4-) hr clialysis. it appears lha! long HD mortality is abollt 50% lowcr. Furthemmorc. this differcnce is cxpluined by a largo ≠ in CV mortality is 3fold lower in Long HD.

Now. ir wc split our own population in 2 cqual cohons of pts according to the median preHD MAP.(integrated valucj thc subgroup with the lowest BP has a significantly lower mortality than thc othcr subgruup. This differcnce in survivnl is mostly explaincd by a large difference in CV mortality: 12.6 vs 28.5 CV dcaths/ 1111111 pr-yrs.

So. long HD nllows for a long survival. This long survivnl is mainly due to a low CV rnortality, Thc rnain Ieature 01' long HD which could explain this rcsult is the BP control.

Now is BP control really good in long slow HD ?

Overa!l SP control is quile good witholll need for antiHT drags. Tassin mean casual preclialysis BP is 128 ovcr 79 within normal range according to Sixth Joint Naliona! Commiltee on BP cval. Ambulatory BP monitoring valucs are also within normal rangc as defined by Slaessen except rOl'the absence 01'noclurnal dip in abollt 50% pts.

This is not a center elTcct.

- the samc control 01' SP withaut ami HT clrug was achieved in 90% of pts in the early 70's

and is still by thosc who continue using long HO toclay...

-But also ver)' often by those who usc claily dialysis whether shon or long achieve a betler

than usual control 01' BP

How & Why does a longer (and probably a more frequent) dialysis improve BP control?

NormoTf\ can be reached in long HD by achicving a normal ECV. in other words. DW. This implics a low salt diet to avoid excessive interdialytic \V gain. a reasonablc dial)'satc Na to achicve a nil diffusive sadium balance. and a sulTicient UF . This is lhe mosl powerful tool but it is also the weakest becausc it is limiled by the patient refilling capacity therefore by lime. Let spend some minutcs 011 lhis.

Ouc to the intennittenl naturc 01' HD the pt oscillatcs belwcen a "wet (saline overloadedl statc" just beforc. ami

a "clry" (salino deplctcd) suue just uftcr thc session. Dunng the fcw hrs 01' HD plasma space is UFiltered clown lo a nadir (show), Refilling Ircm intcrstitial space lags sorne hours behind. So at the very end 01' the run the pt is hypovolemic, he returus lo normovolernia a Iew hours luter when refilling is completed. This unphysiology of íntermittcnt HD is a critica] issue which lcads alternatively to hypertension und hypotcnsion.

To complete this view 1 rnust point at the fact that long slow HD not only reduces HTA but also OTA cpisodes. As displaycd here hypotensivc cpisodes prevalence is lcss in long than in short HD scssion. It is clcur in our own unit when cornparing Shr (7% OTA) to 5 hr (13%) sessions. but even more Ior evcn shoner sessions (20% or more OTA),Thc reduction olbol.h HTA and OTA by a longer (01" probably more frequenu session has a logic,

When session lime dccreases. UF rute is iucreuscd & aTA gets more common. This has ≠ effects: Thc pt has a pOOl' pcrception & ucccptance al' HD &asks [or shorter sessionx-Thc RN has to cut down the UF rate/givc saline so that prescribed D\V is not achieved. The physician wrongly recvaluate DW. Orten he increases dialysate Na which reduces the dilTusive loss of Na. & leads to increased osmolality. thirst & \\'eight gain. Altogclher the pt does not get 10 DW but is overloadcd & HT. He needs moreUF. cventually antiHT drugs which potentiate funher OTA. Intcrdialytic H1' & intradialytic aTA keep on amplifying each olher in a vicious circle...

Does HTA impact on mortality in HD? The qllestion sOllnd curious given Framingham and many olher studies evidence in non-uremic patienls. and the natural answcr is

YES HTA incrcases morlality in dialysis! many studies (a few of them only are displayed here) have shown that mortalily decrcases wilh control 01' HTA

According to these studics HT is very common in HD. it is a risk factor ror slroke. coronary disease. left ventricular hypenrophy and congestive heart failure. And it is 01' note that mOl1ality associated with hYPcl1ension is a longtcrlll effect (≥1O years).

On the other hand. according to others studies. sollle 01' thclll shown here. lhe relationship between HTA and 1110rtality is NOT cstablished. And accorcling lo sevcral 01' them. conversely. it is OTA and not HTA. which is related to mortality. \Vhat can be said about this paradox? and first. what do we know about aTA on dialysis'?

Firsl aTA (excluding 01' course hypolcnsive episodes during the session) is nol very C0111mon in HD. it is a l11arkcr 01'poor cHnical condition: especial1y CHF or frailty. A low BP especially diastolic may be as ror non-uremic pts a coronary risk factor but a causal rclationship is not established. The mortality associaled with hypotension is mostly short-term.

So which is the killer? HTA or ÜTA?

Altogclher ir we plot the monality (yellow line) against MAP. the lowcsl mortalily correlates with nor1110tension. Mortality is higher in I-ITA. but also with hypotcnsion. In fact this U curve is misleading: -1sl bccause we artificially display 011 the sarne curve al! mortality whether short-(OTA) or long-term (HTA): -2nd becuusc ≠ studies use ≠BP estimares lo correlato with monality. 1 shall illustratc tbis sccond pcint with our own population.

Thix is Tassin KM mortnlity curve as a function 01' BP in 3 sub-groups 01' pls according to their mean predialysis MAP calculuted al! ovcr their mairuenuncc dialysis time: thc low BP subgroup (grecnj has the best survival. the high BP subgroup rorange: the worst, the intermediare. an íntermediato survival. lt is something 1 alrcady presentecl earlier. Now if wc iake for the sume pts iheir initial predialysis ivIAP as predictor,

We come out with an inverse correlution: initially the pts with a low initial Máf> (grcern have the highest morrality & conversely. Alter 5-6 yrs 01' FU this rclationship inverses. One musl point al the Iact that al start 01' HD when 90% 01' pts are HT, a low BP is a marker 01' severe heart diseasc or frailty which correlates with **early mortality.** Mazzucchi from Uruguay showed the same thing in a recent paper (but morlality was...).

So altogether aTA is a marker of short-term 1l10rtality. HTA is a cause of long-term mortality. the same U curve pattern has bcen described in non urcmic patients.
Anyway the queslionable risk induced by hypotension is not a mandate to undertreal HTA whose risk is well establishcd,

1 llave 2 remaining questions to address: the Jst (me: ls ECV conlrol the ncccssary and sulTcient condition al' SP control in HD?

A normal SP is a mandatOI)' condition to assert that D\V has been achievcd: as a maller 01' fact a Na+ (ECV) overloaded patient is almost always hypertensive. a hypertensive !-ID patient is almost always Na+ (ECV) overloaded and a normotensive HD patient is almost always at dry weighI. BuL.

A reduced or normal ECV can coexisl with an increased SP (while coat effect. rcnovascular HTA. pheochromocytoma. hypercalcemia...), and on the other hand an incrcased ECV can coexist with a normal 01' decreased BP (antihypertensive Tl. CHF and so forth...).

So, Volmne Xs is by far lhe lirsl delerminanl of HTA in dialysis but othcr factors do exist that must he kept in mind.

2nd Question no\\': ls BP eontrolthc necessary and sufficient concJition 01' a low cardiovascular morbidity and lllortalily on HD. !-Iere the ans\Ver is 01' course NO.

Fol' instance as suggcsted recently by Block a high serum phosphorus and/or CaxP product is correlated \Vith a high CV Illorlality 011 HD. As an illustration 1 comparcd here the CV mortality in 2 Tassin subgroups of plS adjusted rol' age. DI'\l and CV comorbidity & BP. It is signifícantly lower in pls whose prcdialysis serllllll phosphorus is normal lhan in lhose where it exceeds 1.6 ml110l per liter. Olher

Iactors do affect CV morbidity and mortality,

Some are Iinked lo the treatment others to the patient, his Jire style, his discase. his comorbidity, and so forth. These Iactorsprobably explain why in spite 01' a ver)' good BP control cardiovascular problems continué to plague long HD pts. Among them lack of nocturnal clip. vascular calcifcations, LVH that probably cxplain why although lower than in standard HD. the CV mortality in Tussin rernuins much higher than in a standard French adjusted population.

To make a long story short, 1 used Tassin data to focus on CV rnorbidity & rnortality factors, and the way dialysis can rnodit'y thern.

But of course optimal dialysis needs additive imerconnected conditions. Out 01' ECV and BP controlan which 1 focused, it needs small and middle molecule large clearances. adequate nutrition, and probably severa! other conditions. Each 01' these ccnditions is rnandutory. Any 01' thern if not fulfilled may wreck the whole ship. But we must keep in rnind that everywhere including in Tassin the CV mortality remains by fur the first cause 01" death. the one we rnust control first. It is on this that we must plan any prospective poliey airuing at beuer results.

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