

Problems of Calcification of Dialysis Fluid with Acidification of 3 mmol/l Acetate

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*How did we deal with
lemons →
when we use
acetate for acidification?*



why acidification?

- Mammals and Man produce a great deal of CO_2 -Gas \rightarrow transported in Blood as HCO_3^- and eliminated via the lungs by diffusion
- This is driven by metabolism (37°C , motion, function of the body)
- CO_2 40 Torr = 1.2 mmol/l acidification

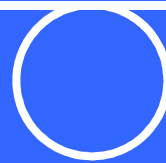
what is the Problem of Bicarbonate Dialysis?



with Acetate Dialysis (1965-1978) you *never* have a Problem with Calcification - there is only the exceeding of the metabolic capacity of the Liver

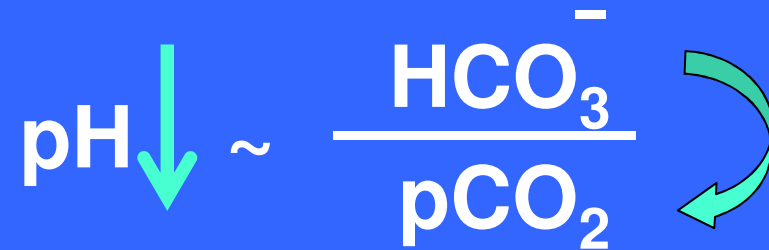
in Bicarbonate Dialysis you have the alternative between Calcification or CO₂ Overload

Problem: short time of HD Treatment (> 12 – 24 h per one week with 168 h of living) → Buffer Concentration was set to 32 mmol/l

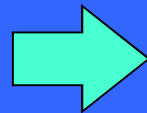


**Acidification in Bicarbonate
Dialysis - but how?**

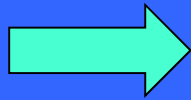
Acidification and its relation to pH?



Addition of acid



partial transformation
from HCO_3^- to CO_2



That is how the solubility of
calcium, magnesium & bicarbonate
can be achieved

how the acidification bicarbonate-dialysis was achieved?

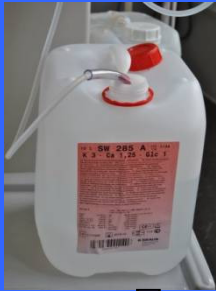
- W. Kolff (1943): acid Na^+ -phosphate
- N. Alwall (1945): carbogen-gas
- since 1978 3 mmol/l acetate
- in France 4 or 5 mmol/l acetate



→ *Perhaps French doctors are better!*

No, they aren't (!): COLD & weaning from Respirator

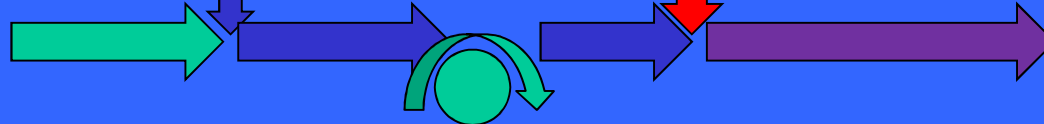
A-Component
3 mmol/l Acetate



BiCart



High-Flux



pH 7.2
pCO₂ 85

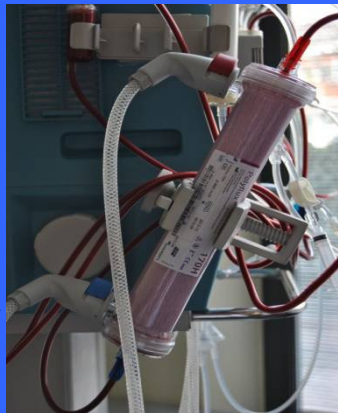
Permeation

De-Air

**Dialysis-
Fluid**

**Treatment
and Calcification**

Dialyzer as Oxygenator (for Exchange of CO₂)



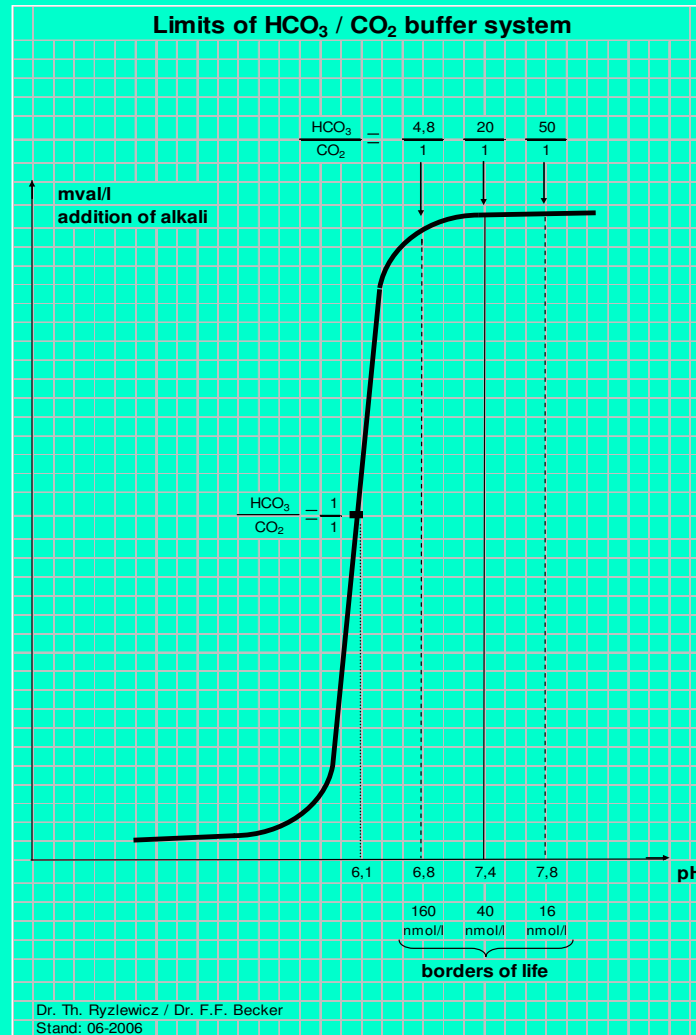
pCO₂ 85 mm Hg
3 mmol/l acid

Calcification



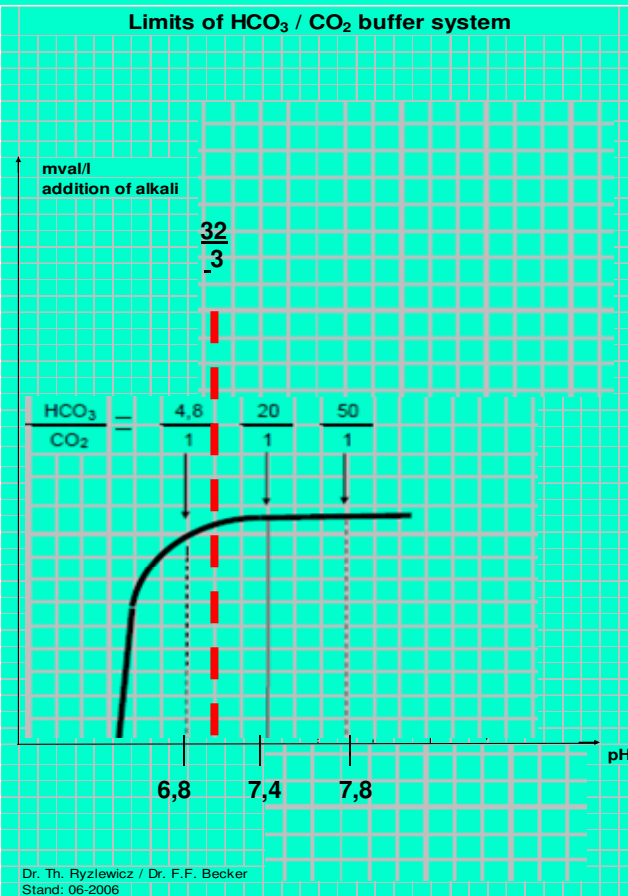
pCO₂ 100 – 130 mm Hg
4 to 5 mmol/l acid

Problems for
COLD-Patients, as well as
for ICU-Patients being on
a respirator



Henderson-
Hasselbalch's
Equation

Limits of HCO₃ / CO₂ buffer system



Henderson-
Hasselbalch's
Equation

... and after the treatment ...



the patient ...
however,
cannot be de-scaled

... the monitor
must be de-scaled
immediately ...

the coefficients of solubility . . .

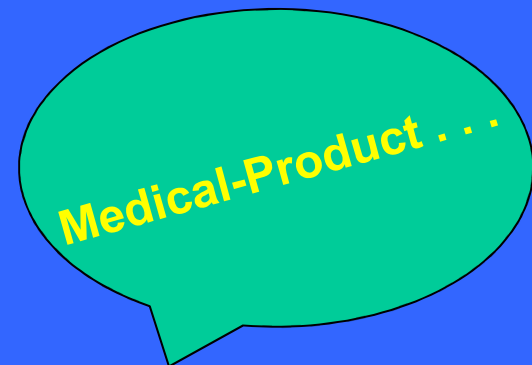
- are known and defined at 20°C and 25°C
- for 37°C they are NOT KNOWN(!)
- Sodium-bicarbonate is soluble (8.4 % or ~ 9 % as BiCart)
- the solubility of Na-bic is dependent on the temperature

the coefficients of solubility . . .



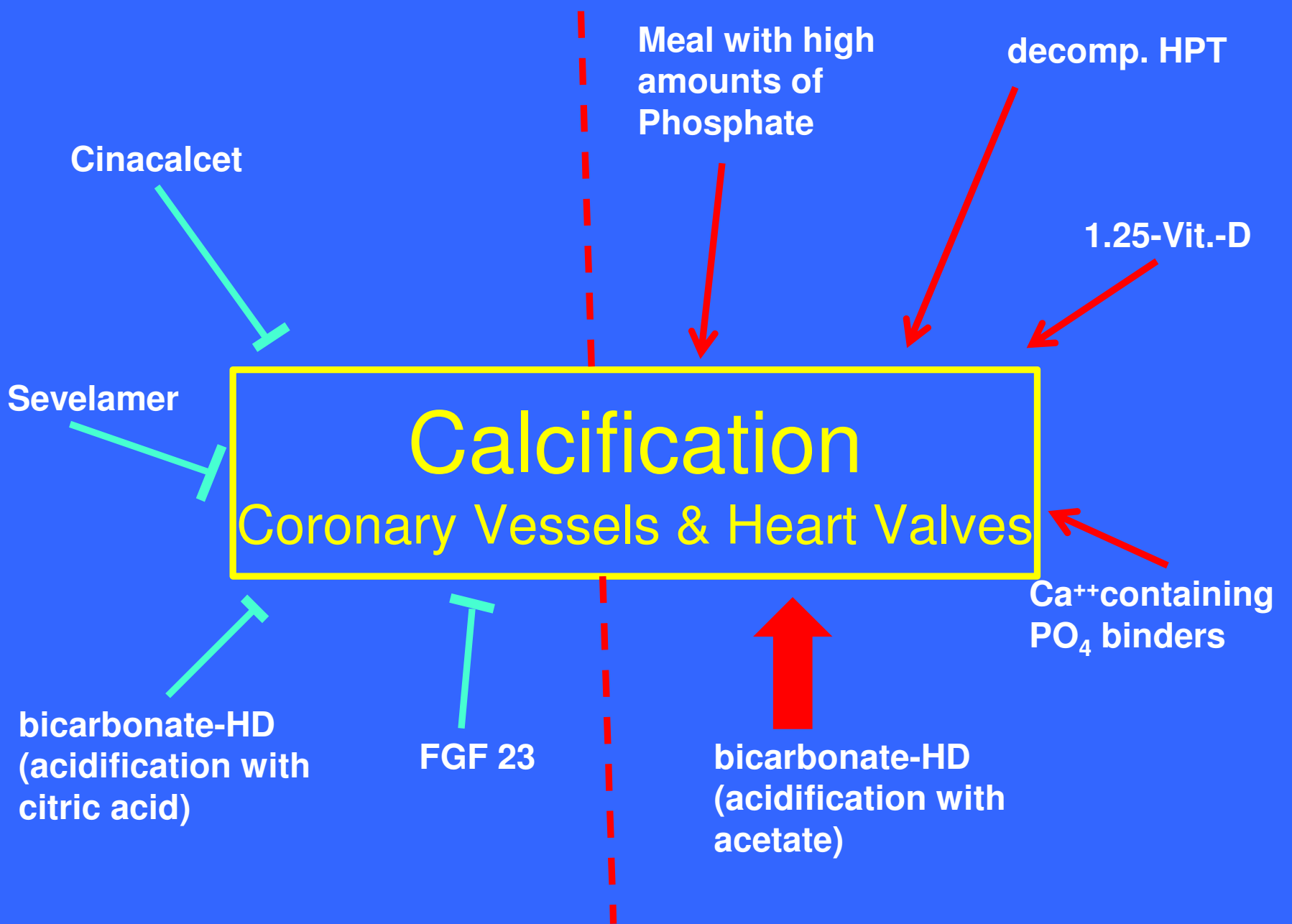
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**as a drug this
prescription of the
dialysis fluid of today
never would be allowed**



Calcification

Coronary Vessels & Heart Valves



Cinacalcet

Sevelamer

bicarbonate-HD
(acidification with
citric acid)

FGF 23

Meal with high
amounts of
Phosphate

decomp. HPT

1.25-Vit.-D

Ca⁺⁺-containing
PO₄ binders

bicarbonate-HD
(acidification with
acetate)

Clearance 15 ml/min: when does the calcification begin?

CKD-4: phosphate-
elimination will be
improved by FGF 23

→ „no phosphate binders“
and
„no calcification“

CKD-5: same as CKD4
Now bicarbonate dialysis
is started
(acetate-acidification)

→ calcification:
→ now the patient needs
„phosphate binders“

the challenge of acidification with acetate:
„calcification or too high pCO₂“

the Solution: acidification with citric acid

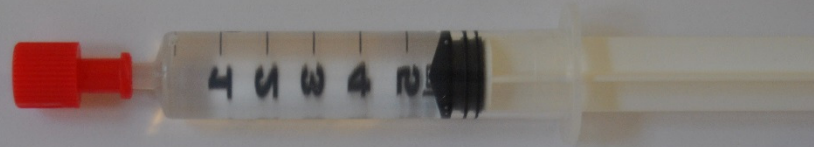


Why?

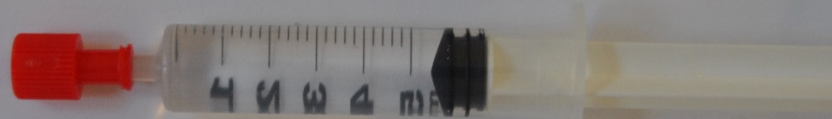
with the same power of acid &
CO₂ production nothing will
calcify because Ca⁺⁺ is
disguised in the chelate lattice

Transparency of a Solution

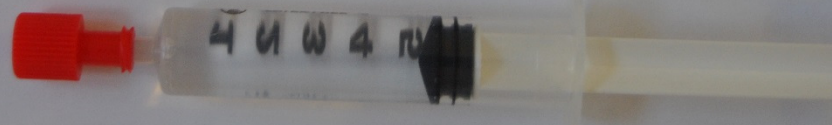
Acetate
Acidification



Citrate
Acidification



NaCl 0,9 %



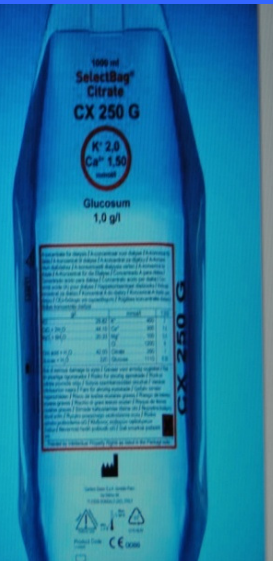
Laymen & Patients
see the difference

Nephrologists
didn't see this

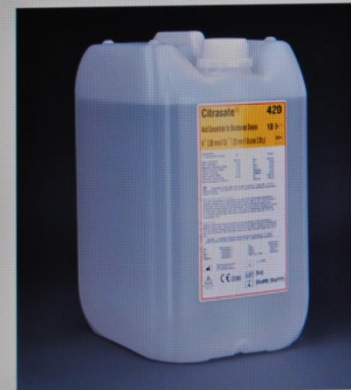
BfArM ignores this

SelectBag® Citrate ist ein einzigartiges azetat-freies Konzentrat, das alle Vorteile von Citrat aufweist. Mit dem BiCart Select Citrate-System ist es ein Leichtes, die optimale Zusammensetzung der Dialysierflüssigkeit zu erreichen. Natrium- und Bikarbonat Spiegel werden anhand der von Ihnen festgelegten Einstellungen genauestens kontrolliert. Dank des SelectBag Citrate-Beutels können Sie die Zusammensetzung von Kalium, Kalzium und Glukose ganz einfach anpassen.

- Verbessertes Säure-Basen-Gleichgewicht
- Leichtere Individualisierung von Elektrolyten
- Weniger thrombogene Dialyse
- Weniger Inflammation
- Bessere Behandlungsverträglichkeit
- Bessere Behandlungseffektivität



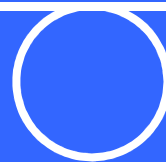
verbessert die Behandlung aller Hämodialysepatienten



Advanced Renal Technologies, Inc. (ART) Washington, USA, hat eine neue Dialysezusammensetzung entwickelt, die auf die Bedürfnisse der Patienten zugeschnitten ist und die Effektivität der Behandlung verbessert. Mit **Citronensäure** als säuerndem Wirkstoff ist dies die erste bedeutende Veränderung der Dialysatzusammensetzung seit mehr als 40 Jahren, die sich von den herkömmlichen Formulierungen, die Essigsäure enthalten. Sie ist durch die FDA für alle Patienten freigegeben, ist bereits auf dem Markt erhältlich und wird in vielen Kliniken auf der ganzen Welt eingesetzt.

Patienten Vorteile:

- Ersetzt oder verringert Heparinbedarf bei CRF Patienten
- Verbessert Dialysesdosierung Kt/V
- Korrigiert Acidose
- Verringert Post-Dialyse-Blutungen



Acidification with Citric Acid

Acidification with Citric Acid



Select Bag Citrate
1.0 mmol/l
Citric Acid

Citrasate
0.8 mmol/l
Citric Acid
& 0.3 mmol/l Acetate

	3.0 mmol/l Acetate	4/5 mmol/l Acetate	0.8 mmol/l Citric Acid 0.3 mmol/l Acetate (MTN)	1.0 mmol/l Citric Acid Gambro
Problem	Calcification	high pCO ₂	./.	./.

**Survey of the different possibilities
for acidification**

what should be taken into account when acidifying with citric acid?

- NOTHING will calcify (neither the patient nor the monitor)
- Ca^{++} in the dialysis fluid must be raised a little (Citric Acid – after having passed the dialysis membrane – will bind a smaller part of Ca^{++})
- so measurement of Ca^{++} after switching the dialysis fluid is reasonable for the first time
- the dosage of heparin can be reduced to 50 %

*Is there a problem of communication
when acidifying with citric acid?*

Indeed, this exists:

the acidification with citric acid is *not well understood by many doctors.*

nevertheless, a discussion concerning the concentration of Ca^{++} in the dialysis fluid is continued . . .

why is the acidification with 1.0 mmol/l
citric acid a good concept?

Do it right the first time! (RH Herbst)

- no further elevation of $p\text{CO}_2$
- no calcification at all
- good anti-thrombogenic effect (< Heparin) ↓

equal acidification with 3.0 meq/l

Acetate

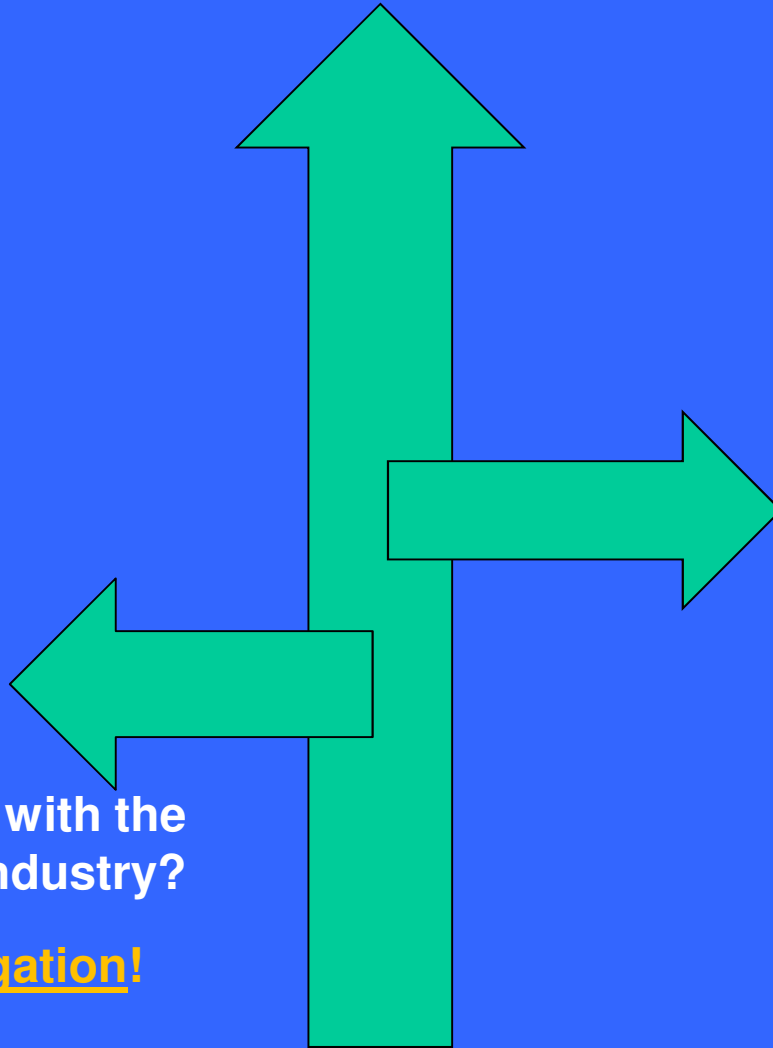
- here only one principle is working:
 - a (smaller) part of bicarbonate will be transformed into CO_2

Citric Acid

- at first the same effect as with acetate
- second effect by disguising Ca^{++} and Mg^{++} by the chelate lattice of citric acid → product for solubility of Ca^{++} x citrate and Mg^{++} x citrate will not be reached

?

Strategy



Lecture / Congress?

→ without obligation!

Discussions with the
Industry?

→ without obligation!

Acidification with Citric Acid

3 possibilities

- Study
- Prohibition of the 3 mmol/l acetate-acidification (> BfArM)
- one concerned Patient (> chemist)
- Information of the doctor doesn't work here → the theme is too complicated!

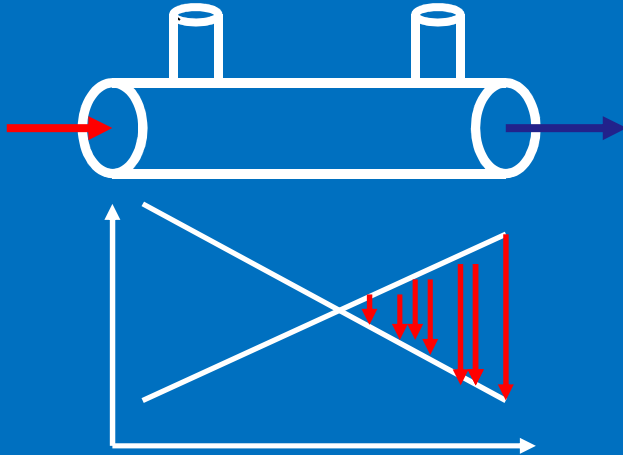
why a Chemical Evaluation is necessary?

- the Problem of Calcification with 3 mmol/l Acetate Acidification is a Problem of Solubility
- this never can be judged in a qualified way by Physicians
- there does exist the Prescription with 1 mmol/l Citric Acid without any Calcification
- the Medical Authority BfArM Institute ignored the Chemical Evaluation without a serious reason

Steps to reach a Chemical Evaluation:

- Oct. 2012 Letter to BfArM Institute Germany
Result: Reference Number, Proposal to discuss this at DGN
- Dec. 2013 Letter of a Medical Lawyer
→ no Result(!)
- May 2014 Letter to the German Minister of Health (> Supervision of the BfArM)
- May 2014 Report to FDA (> VMDR & 3500A)

Conclusion



Backfiltration 8 ltr.
or online-HDF up to 30 ltr.

Calcifying Fluid

2 well known
Chemists . . .

. . . did not mention the
Calcification with
Acetat-Acidification . . .

**. . . related with
Dialysis Industry**

BfArM Institute
Medical Product

. . . refuses a Chemical
Evaluation

**Everything is
allowed with a
Medical Product**



FDA is involved (> VMDR & 3500 A for Chemical Evaluation)

We have to say what we think

We have to do what we say

What we do should reflect this

Alfred Herrhausen

1930 - 1989