Chairperson, dear colleagues. The question I have to address is, are all iron preparations equal? The answer is very simple, the answer is no.
In this slide I have summarized some of the iron preparations used orally or intravenously for the treatment in patients with CKD. You are familiar with the fact that we have different oral iron preparations. We had in the past high molecular weight iron dextran and we are still using low molecular weight iron dextran. In Europe we are mostly using iron gluconate and iron sucrose, in some papers also mentioned as iron saccharate. I personally prefer iron sucrose. More and more data are generated with iron sucrose similars, ISS. In several European countries Ferric polymaltose or Ferric carboxymaltose is available. In countries outside Europe Ferumoxytol is available and used. A new iron compound is iron isomaltoside 1000 and iron HES may probably come in next time or soon to the market.

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### Common oral iron preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Dose (mg)</th>
<th>Elemental Iron Content (mg)</th>
<th>5000-mg Dose Cycle (Tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulphate</td>
<td>324</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300</td>
<td>36</td>
<td>140</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>100</td>
<td>33</td>
<td>150</td>
</tr>
</tbody>
</table>
A few words about common oral iron preparations. I personally find that it may create confusion for us in our daily therapy that a certain dose is indicated for example, for iron sulphate per tablet 324mg or for iron gluconate 300mg. But if you look more in detail you see these preparations differ markedly with respect to elemental iron content and usually the body cannot utilize more than 200mg of elemental iron per day and if you select iron sulphate for a certain dose of iron therapy, your patient needs a tablet cycle of 75. If you select iron gluconate, your tablet cycle is twice as high. If you look on paper where intravenous iron or oral iron is used or compared between each other, this is to my knowledge very confusing that in several papers it’s only the amount of iron per tablet indicated but not the amount of elemental iron and you do not have in some papers any suggestion about which type of iron is discussed.

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Iron preparations for intravenous iron therapy in CKD patients (present and future) (1)

- Low molecular weight iron dextran  
  (Cosmofer®, up to 20 mg/kg (5 hours), test dose required)
- Iron sucrose (iron saccharate)  
  (Venofer®, up to 500 mg (4 hours), 10-100 mg within 1-10 min, test dose recommended)
- ISS (iron sucrose similars)  
  (FerMed®, recommendations as for Venofer®)
- Ferric gluconate  
  (Ferlecit®, 62.5 mg–125 mg within 5-10 min)

Going into detail through iron preparations used for IV iron therapy in CKD patients at present and also in the near future, we have low molecular weight iron dextran. This compound can be administered in a dose of up to 20 mg/kg within 5 hours and as for all dextran preparations a test dose is required. Iron sucrose can be used up to 500mg as a single infusion up to 4 hours. I do not use this high dose iron sucrose therapy and I also don’t recommend this type of sucrose administration. We prefer low dose iron sucrose therapy particularly, in haemodialysis patients where you can inject 10mg or 20mg/ haemodialysis therapy within 1 or 2 minutes or 100 mg in 10 minutes even if the test dose is recommended to my knowledge nobody performs a test dose. There is on-going discussion on iron sucrose similars are these generic or not or are these more complex molecules which are better called iron sucrose similars? My position is clear these are iron sucrose similars and not generic, I will come back to this issue.

In many countries in Europe, as I mentioned before, iron gluconate is used. The allowed dosage is 62.5 mg/ injection in the US, 125 mg are allowed to be injected within ten minutes. If you look at several studies published in papers such as KI, you will be shocked to see how many patients receive 200mg of iron gluconate in less than one minute and so many adverse events on IV iron therapy reported in the literature are related to inadequate use of the IV iron compound. You see among these iron preparations completely different dose recommendations and the explanation is that the stability of these complexes are very, very different. This is important when we go later on through in vitro or in animal experiments.

Slide 5
For Ferric polymaltose or carboxymaltose up to 15mg/kg can be injected within 15 minutes. The maximal recommended dose is 1000mg. At present we do not have enough data for the dialysis patient population. So the recommended maximal single dose for the dialysis patient population is 200mg. I'm sure further studies are on-going to clarify the issue, can we go up to 500mg or even to 1000mg per injection also in the dialysis population?

Ferumoxytol can be very rapidly administered, approximately 500mg within one minute. Iron isomaltoside is, as I said before, a new compound which can be administered as a bolus in a dose between 100-200 mg. Again the maximal dose is 20mg/kg within 60 minutes. This is a more linear molecule than iron dextran and probably less immunogenic, a test dose is not required. The final product, which I won’t discuss, is iron HES and dose-finding studies are under investigation.
This is an evaluation which George Baillie and I performed a few years ago where he collected data, adverse event reported data with hypersensitivity and serious events reported to the FDA. I collected the data reported in Europe to the Uppsala registry in Sweden. I should say not all European countries report to the Uppsala registry. What you can see over time is that the use of ferric gluconate remains constant also as does at far lower levels iron dextran use but iron sucrose was a preparation which has increased markedly on the market during the last years. This probably always a very safe iron compound.

Here you can see serious adverse events between iron sucrose, between iron gluconate and iron dextran in Europe and in North America and in both countries together. It is easy to see that the highest severe reported reaction, for example, hypersensitivity or
anaphylaxis or other severe events are related to iron dextran. Interestingly, we summarised the data with low molecular weight and high molecular weight iron dextran compounds because the reported incidences were not very different.

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Anaphylaxieraten und Prozentsatz anderer schwerer Nebenwirkungen pro Million 100 mg Dosisäquivalente intravenöser Eisenpräparate


Here you can see a subanalysis of the reported severe events with respect to anaphylaxis, with respect to allergy between Europe and North America and both together and again anaphylaxis and allergic reactions were actually highest reported with iron dextran.

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KDIGO Chapter 2:
Use of iron to treat anemia in CKD

Cautions regarding iron therapy

2.3: When the initial dose of IV iron dextran (1B) or IV non-dextran iron (2C) is administered, we recommend that resuscitative medications and personnel trained to evaluate and treat serious adverse reactions be available.
This is important, the recent KDIGO guideline recommend: when the initial dose of IV iron dextran or any other known iron dextran is administered, we recommend resuscitative medications and personnel trained to evaluate and treat serious adverse reactions should be available as we have seen from this slide allergic or hypersensitive reactions are not excluded with non-iron dextran compounds.

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![Comparison between low molecular weight iron dextran (CosmoFer®) and iron HES (Feramyel®) during the registration study in ND-CKD patients receiving approx. 800 mg IV of each drug](image)

These are newer data which we have not published so far. You see we performed registration studies between low molecular weight iron dextran CosmoFer and iron HES in non-dialysis CKD patients in this registration study. Both patients received approximately 800mg iron IV to demonstrate non inferiority of iron HES in comparison to iron dextran.

You see a similar increase in serum ferritin not a surprising observation but you can also see an oversaturation with iron dextran in comparison to iron HES. This must be confirmed by determination of non-transferrin bound iron content in both iron preparations and you can also see here a difference. Whereas, none of the patients with iron HES had an anaphylactic reaction, one patient, a 30 year old patient had a severe anaphylactic reaction after receiving the test dose of iron dextran. Of course, far more data are necessary to evaluate the safety proof of iron HES.

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A comparison between two iron sucrose preparations was recently performed by doctor Rottenbourg and colleagues in 75 haemodialysis patients, a comparison was made over a period of 27 weeks in both arms with iron sucrose and iron similars. You can see patients with the originata iron sucrose had significantly higher haemoglobin levels in comparison to the iron sucrose similar preparation, had higher transferrin saturation, needed 13.5% lower iron during this time period of 27 weeks and had a significantly, approximately 12% lower need for ESA therapy. So there may be significant clinically relevant difference between iron sucrose and iron sucrose similars.

Recently some in vitro or once more in vitro data were performed comparing different iron formulations with different structures on cellular level of doctor Saga and his co-workers. I do not really like this data and I will show you why. Iron sucrose, iron
gluconate and Ferumoxytol were compared exactly with the same dose also with exactly the same concentration what in my view is not valid because we use gluconate only in approximately a 10-fold lower dose per injection as compared to Ferumoxytol. With this partially artificial data you can demonstrate a higher cytotoxicity with HK-2 cells, with iron sucrose as compared to iron gluconate and not surprisingly, the most stable or the lowest cytotoxicity is observed with the most stable iron content and similarly the expression of redox sensitive genes. For example, with monocytes, chemoattractant proteins are different between these compounds, must be different because they are in my opinion not compared on an adequate level.

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Renal cortical neutrophil gelatinase-associated lipoprotein (NGAL) induction post-Fe injections

and the same is true if you inject animals with an identical amount of different iron compounds with different stabilities, you certainly will have a time-dependent increase in NGAL as a marker for renal toxicity if you use the by far more stable compounds in the same concentration as unstable compound.

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Finally, a further example comparing non-transferrin bound iron in patients injected with 100mg low molecular weight dextran in comparison to 100mg iron sucrose. You see a similar increase in non-transferrin bound iron. So in both compounds transient free iron may occur. Here is an oxidative stress parameter with this oxidative stress parameter there was clinically with adequate dosage no difference between low molecular weight iron and iron sucrose.

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Are all iron preparations equal?
Summary

- Structural differences in currently employed Fe formulations
- Differences in complex stability resulting in different maximally allowed doses to be administered
- Differences in serious adverse events and the risk for anaphylaxis
- In vitro and in animal experiments with supra-normal dosages, differences in
  - prooxidant effects
  - cytotoxicity
  - redox-sensitive gene expression
- Safety and efficacy of intravenous iron compounds in daily clinical use

To summarise, when I should answer the questions are all iron preparations equal? As I said before, the answer is no. We have structural differences in currently employed iron formulations. We have differences in the complex stability resulting in different maximally allowed doses to be administered ranging from 62.5mg/injection up to 20mg/kg with another
compound. We also have differences in serious adverse events and the risk of anaphylaxis *in vitro* and in animal experiments with supra normal dosages. In my opinion with some artificial comparisons we also have differences in the pro-oxidative effects, cytotoxicity and redox-sensitive gene expression but nevertheless, we can state that all iron compounds used intravenously for our patients in the daily practise have a high safety and a high efficacy profile.