Patient persistence with antihypertensive drugs in France, Germany and the UK

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Declaration on Conflict of Interest

The presenter is a full-time employee of Daiichi Sankyo Europe
Hypertension - a major public health problem worldwide

Background

• Hypertension is an important factor contributing to the risk of cardiovascular diseases and death

• Geographic variations regarding epidemiology of the hypertension worldwide

• The age- and sex-adjusted prevalence of hypertension for the European average is approximately 44%
  ➢ (highest prevalence of 55% in Germany and lowest in Italy, 38%) compared with 28% in USA and Canada

Patient persistence is crucial for effective blood pressure control and reduces the burden of hypertension.

Treatment

- **Effective blood pressure (BP) control** is achievable in the majority of patients and can significantly **reduce the burden of hypertension** including early mortality.

- **Patient persistence** is crucial for successful BP control. Persistence with drugs **differs between antihypertensive drug classes**.

- The 2007 ESH/ESC guidelines list following classes of drugs considered appropriate for the first-line therapy in hypertension: diuretics, beta-blocking agents (BB), calcium antagonists (CCB), angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II antagonists (ARB).

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Persistence in hypertension: findings of key publications published within the last 5 years

Research status

Compared with free-drug combinations, fixed-dose combinations of antihypertensive agents are associated with a significant improvement in compliance and persistence (Gupta, 2010; Bramlage, 2009; Zeng 2010)

Persistence was higher with ARBs than on any other drug class (Bramlage, 2009)

Persistence with treatment was higher in patients treated with ARBs and ACE inhibitors (Veronesi, 2007; Borghi, 2007; Hasford, 2007)

This retrospective database analysis aimed
• to evaluate the **prescription patterns** and **persistence** of
  patients receiving different classes of antihypertensive drugs in
  France, Germany and the UK.
IMS Disease Analyzer™ databases hold data from representative sample of GP practices in France, Germany and the UK.

**Methods**

- This retrospective study analysed prescription data collected by general practitioners (GPs) in France, Germany and the UK using three longitudinal databases of the IMS® Disease Analyzer.

- **Patient populations**
  - **Prescription patterns:** patients with hypertension (ICD-10 code I10) initiated on different ATC classes of antihypertensive drugs during the period 09/2009-08/2010.
  - **Persistence:** patients with hypertension (ICD-10 code I10) initiated on different ATC classes of antihypertensive drugs during the period 09/2008-08/2009, with a follow-up of at least one year.

- **Antihypertensive drug classes**
  - diuretics, beta-blocking agents (BB), calcium antagonists (CCB), ACE inhibitors (ACEI) and angiotensin II antagonists (ARB)

- **Persistence** was defined as the proportion of patients remaining on their initially prescribed therapy for 1 year.

Demographic characteristics of patients with hypertension in France, Germany and UK were comparable.

**Results – Treatment Pattern**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Prescription patterns</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>67,778</td>
<td>406,888</td>
<td>119,574</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>65.9 (13.2)</td>
<td>66.0 (14.1)</td>
<td>68.1 (13.6)</td>
</tr>
<tr>
<td>Gender (f/m) in %</td>
<td>53.7/46.3</td>
<td>53.8/46.2</td>
<td>53.9/46.1</td>
</tr>
<tr>
<td><strong>Persistence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>11,872</td>
<td>59,774</td>
<td>18,661</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>65.8 (13.1)</td>
<td>66.0 (13.7)</td>
<td>66.1 (13.7)</td>
</tr>
<tr>
<td>Gender (f/m) in %</td>
<td>53.1/46.9</td>
<td>55.7/44.3</td>
<td>52.9/47.1</td>
</tr>
</tbody>
</table>

* patients with hypertension who were initiated on different ATC classes of anti-hypertensive drugs in the period 09/2009-08/2010 with data available for at least the following 12 months.
Prescription patterns varied among countries

Results – Prescription Pattern

### Prescription Patterns

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>Germany</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of hypertension</td>
<td>67,778</td>
<td>406,888</td>
<td>119,574</td>
</tr>
<tr>
<td>Treatment of hypertension</td>
<td>89.3%</td>
<td>85.4%</td>
<td>94.0%</td>
</tr>
<tr>
<td><strong>Prescriptions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>20.0%</td>
<td>28.0%</td>
<td>49.3%</td>
</tr>
<tr>
<td>BB, plain</td>
<td>30.2%</td>
<td>49.7%</td>
<td>28.5%</td>
</tr>
<tr>
<td>BB, combination</td>
<td>5.1%</td>
<td>5.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>CCB, plain</td>
<td>25.9%</td>
<td>27.2%</td>
<td>43.4%</td>
</tr>
<tr>
<td>CCB, combination</td>
<td>1.6%</td>
<td>0.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td>ACEI, plain</td>
<td>16.5%</td>
<td>37.4%</td>
<td>51.0%</td>
</tr>
<tr>
<td>ACEI, combination</td>
<td>12.4%</td>
<td>19.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>ARB, plain</td>
<td>25.0%</td>
<td>12.9%</td>
<td>21.4%</td>
</tr>
<tr>
<td>ARB, combination</td>
<td>25.9%</td>
<td>14.4%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

ACEI: ACE inhibitors; ARB: angiotensin II receptor blockers; BB: beta-blocker; CCB: calcium channel blockers

Prescriptions may overlap and add up to more than 100%!
Highest persistence was achieved by fixed-dose ARB comb. in France and Germany, and by plain ARBs in the UK.

Results – Persistence

- Persistence with hypertensive drugs after 12 months – percentage of patients

<table>
<thead>
<tr>
<th></th>
<th>France % of patients</th>
<th>Germany % of patients</th>
<th>UK % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI, plain</td>
<td>48.5%</td>
<td>58.0%</td>
<td>65.6%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>50.8%</td>
<td>55.3%</td>
<td>66.6%</td>
</tr>
<tr>
<td>CCB, plain</td>
<td>52.2%</td>
<td>56.1%</td>
<td>67.1%</td>
</tr>
<tr>
<td>BBs, plain</td>
<td>58.1%</td>
<td>67.8%</td>
<td>65.8%</td>
</tr>
<tr>
<td>ARB, plain</td>
<td>52.8%</td>
<td>63.5%</td>
<td>78.2%</td>
</tr>
<tr>
<td>ARB, combination</td>
<td>61.9%</td>
<td>71.0%</td>
<td>67.1%</td>
</tr>
</tbody>
</table>
Limitations

• Persistence was measured indirectly based on prescription information, which means that the true extent of treatment duration or dosing frequency could be under- or overestimated.

• Substantial percentages (about 80%) patients were not included in the analyses of persistence, because they did not have at least one-year follow-up data.

• It was assumed that data in the database were missing at random, thus no missing data imputation was performed.

• The reasons for discontinuation were not analyzed (e.g. side effects).
Higher persistence in the UK may be due to better medication-taking behaviours among UK patients

Conclusions

Overall, persistence with the most frequently prescribed antihypertensive drugs appears to be better in the UK than in France and Germany. This might be influenced by factors such as physician-patient communication, social environment and health insurance status.

The best persistence is demonstrated for plain ARBs in the UK and fixed-dose ARB combinations in France and Germany. The relatively favourable safety profile of ARB therapy might influence decisions by physicians. These results are similar to results of a systematic literature review by Bramlage et al. showing higher persistence with ARBs compared with ACEIs, CCBs or diuretics.

Differences between countries as well as between classes of antihypertensive drugs indicate room for improvement of hypertension management strategies.

Thank you very much for your attention
13,437 patients in France, 68,341 patients in Germany and 16,165 patients in the UK were identified.

Results – Analysis Pattern

Eligible for analysis:
13,437 patients in France, 68,341 patients in Germany and 16,165 patients in the UK

Mean age and gender distribution was comparable between countries for prescription patterns and persistence

Results shown with sufficient sample sizes (n > 100) for: diuretics, plain BBs, CCBs, ACEIs; ARBs, plain and combinations
The mean duration of persistence per patient...

...in **France** varied it from 249.1 days with plain ACE inhibitors to 289.1 days with ARB combinations;

...in **Germany** it varied from 265.0 days with diuretics to 305.4 days with ARB combinations;

...while in the **UK** is varied from 283.7 days with diuretics to 314.6 days with plain ARBs.
What is the difference between persistence and compliance?

Definitions of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Workgroup:

- **Compliance** is defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen”
- **Persistence** is defined as “the duration of time from initiation to discontinuation of therapy”.

- We calculated the proportion of patients who remained on their initially prescribed therapy after one year. The duration of persistence in our study was calculated as the last prescription date of the initially prescribed therapy plus the duration of the drug supply received with the last prescription minus the index date. Moreover, the average persistence related to the one year after the index date was determined as the number of days patients remained on their initially prescribed therapy.

Why is persistence considered so important for blood pressure control?

- Patient persistence, the continuity of taking medications, is crucial for successful BP control. Persistence is improved by using fixed-dose combinations instead of unfixed combinations.
- Low persistence leads to higher overall cost.
- A pill not taken cannot be effective. As hypertension is a chronic disease, only the constant intake of medication can lead to the required protection and avoidance of more dramatic clinical events like myocardial infarcts.


What are the studies showing that lack of persistence results in poor blood pressure control or poor outcomes?

• The influence of compliance and persistence for reaching the therapy goal in the treatment of hypertension is well documented.
• Compliance and persistence directly influence the effectiveness of hypertension therapy regimes.
• Mathes et al. (2010) identified a correlation between the persistence and the risk for a first hypertension-associated event.
• Bramlage et al (2009) pointed out that higher levels of persistence, often related to more expensive drug categories like ARBs, ACEIs and CCBs, were often associated with lower overall health care costs.
• These savings were associated with a fewer number of hospitalizations for these patients.

What was the intention of the current study? Why did you choose to look at antihypertensive drugs in France, Germany and the UK?

• So far, no data are published which combines country-specific prescription patterns with the analysis of persistence and ARB treatment patterns in European countries.

• Among aspects like the availability of drugs and differences in national guidelines, a cross-country focus will also provide indications to discuss different management strategies for hypertension patients.

• **This retrospective database analysis aimed to evaluate the prescription patterns and persistence of patients receiving different classes of antihypertensive drugs in France, Germany and the UK.** In addition, the ARB treatment patterns were investigated with respect to the use of mono-, dual and triple therapy as well as to the prescription of unfixed and fixed-dose combinations.

• Furthermore, Europe has limited availability when it comes to data analysis and data resources like this, because of different regulations in the respective EU markets.
What is the IMS Disease Analyzer – and what were the three longitudinal bases that your study was based on?

- **IMS Disease Analyzer** (DA) is a database that holds patient data from a sample of GP practice systems.
- This retrospective study analyzed anonymized prescription data collected by GPs in France, Germany and the UK using three longitudinal databases of the DA. The participating GPs continuously recorded general practice activity, prescriptions, hospital admissions, specialist referrals and laboratory test results.
- The DA databases are representative and validated, suitable for pharmacoepidemiological and pharmacoeconomic studies.

How could the show whether patients remained on their initially prescribed therapy for 1 year?

• To analyze **prescription patterns**, the DA databases were searched for patients with hypertension (ICD-10 code I10) initiated on different ATC classes of antihypertensive drugs during the period 09/2009-08/2010.

• To analyze **persistence**, the databases were searched for patients with hypertension (ICD-10 code I10) initiated on different ATC classes of antihypertensive drugs during the period 09/2008-08/2009, with a follow-up of at least 12 months.
What did the results show:
For persistence of different antihypertensive therapies?
For persistence in different countries?

The highest level of persistence is achieved with ARBs (71%) followed by BBs, ACEIs and CCBs. The lowest level of persistence was achieved by patients using diuretics.

France
• The analysis of the data displayed a similar ranking as mentioned above, but a lower overall level of persistence. 12 months after the first prescription, persistence ranged from 48.5% with plain ACEIs to 61.9% with ARB combinations.
• The mean duration of persistence per patient varied from 249.1 days with plain ACEIs to 289.1 days with ARB combinations.

Germany
• Persistence ranged from 55.3% with diuretics to 71.0% with ARB combinations.
• The mean duration of persistence per patient varied from 265.0 days with diuretics to 305.4 days with ARB combinations.
• In France and Germany, the same order of substances with the three highest persistence values (ARBs comb (61.9%/71.0%) > BB plain (58.1%/67.8%) > ARBs plain (52.8%/63.5%) was observed.

UK
• Persistence ranged from 65.6% with plain ACEIs to 78.2% with plain ARBs.
• The highest percentage of patients staying persistent after 12 months was found for ARBs plain (78.1%) followed by ARB combinations (67.1%) and CCB plain (67.1%).
• The mean duration of persistence per patient varied from 283.7 days with diuretics to 314.6 days with plain ARBs.
Why do you think persistence was best for plain ARBs?

• We did not examine the reasons for the favorable rate of treatment persistence with ARB therapy, but we assume that a relatively favorable safety profile (in addition to the clinical efficacy) may be a major contributing factor.
Why do you think that persistence with antihypertensive drugs was better in the UK than France and Germany?

- This might possibly be due to the better medication-taking behaviors among UK patients.
- There is some evidence suggesting the influence of factors on antihypertensive treatment compliance such as the perceived therapy control, coping with therapy barriers, physician-patient-communication, social environment and health insurance status.
- These factors might play important role in persistence as well.
- More studies are needed to answer this question.
What improvements in hypertension management strategies could result from this study?

• In patient cases when persistence and compliance are of high relevance to the treatment accomplishment, ARBs and their fixed-dose combinations may play an important role.

• However, the measurement of specific management strategies was not addressed in our observational study, but we feel that there are other resources available to pragmatically improve treatment dimensions like compliance under e.g. www.hypertensioncare.eu.
What further lessons can you draw from this study?

- The systematic literature review by Bramlage et al (2009) has shown that over a 12-month period, persistence with treatment was generally higher with ARBs (ranging between 42% and 64%), compared with ACEIs, CCBs, BBs and diuretics.

- Our study, based on real-life data from physicians’ practices confirms these findings.

How can this information be used to help clinical practice?

- Inadequate persistence with certain classes of medications should be addressed in the clinical practice, the physician-patient-communication strengthened, awareness among patients about the dangers of non-persistence and non-compliance should be improved, and existing variety of combined medications with flexible dosages in one tablet should be efficiently prescribed and administered.
What further studies are you planning?

- To explore longer follow-up data, e.g. at 24 months after first prescription, to see whether persistence in different medication classes changes.
- To look at the predictive value of current persistence on future persistence, as well as cost implications.
- Swindle et al (2011), based on the retrospective claims data analysis in the US, showed that within ARBs long-term clinical and economic data, outcomes may differ:
  - Treatment with Olmesartan was associated with lower risk of cardiac events and lower healthcare resource utilization and costs versus Valsartan, Losartan, and Irbesartan over a mean follow-up of 2.5 years.
  - It can be relevant to look at persistence and compliance using IMS DA and compare the findings among patients on different ARBs.

  
How could you look at compliance using this data base?

- To assess it indirectly based on the medication possession ratio (MPR), calculated as number of days supplied within the refill interval in relation to the number of days in the refill interval.
Persistence curves for anti-hypertensive drug classes - France

- C3A DIURETICS (2,003)
- C7A B-BLOCKING AGENTS PLAIN (2,173)
- C8A CALCIUM ANTAGONIST PLAIN (2,037)
- C9A ACE INHIBITORS PLAIN (1,435)
- C9C ANGIOTEN-II ANTAG, PLAIN (2,354)
- C9D ANGIOTEN-II ANTAG, COMBINATIONS (1,870)

Share of patients remaining on therapy (%) vs. months after first prescription
Persistence curves for anti-hypertensive drug classes - Germany

![Persistence curves graph](image)

- C3A DIURETICS (11,756)
- C7A B-BLOCKING AGENTS PLAIN (14,679)
- C8A CALCIUM ANTAGONIST PLAIN (10,351)
- C9A ACE INHIBITORS PLAIN (13,763)
- C9B ACE INHIBITORS COMBINATIONS (6,674)
- C9D ANGIOTEN-II ANTAG, COMBINATIONS (4,309)
Persistence curves for anti-hypertensive drug classes - UK

- C3A DIURETICS (4,079)
- C7A B-BLOCKING AGENTS PLAIN (2,147)
- C8A CALCIUM ANTAGONIST PLAIN (4,555)
- C9A ACE INHIBITORS PLAIN (4,820)
- C9C ANGIOTEN-II ANTAG, PLAIN (1,521)
- C9D ANGIOTEN-II ANTAG, COMBINATIONS (140)