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Does hydroxyapatite coating of uncemented cups improve long-term survival? An analysis of 28,605 primary total hip arthroplasty procedures from the Nordic Arthroplasty Register Association (NARA)

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Objective: It is unclear whether hydroxyapatite (HA) coating of uncemented cups used in primary total hip arthroplasty (THA) improves bone ingrowth and reduces the risk of aseptic loosening. We therefore investigated survival of different uncemented cups that were available with or without HA coating.

Method: We investigated three different cup types used with or without HA coating registered in the Nordic Arthroplasty Register Association (NARA) database that were inserted due to osteoarthritis (n = 28,605). Cumulative survival rates and adjusted hazard ratios (HRs) for the risk of revision were calculated.

Results: Unadjusted 13-year survival for cup revision due to aseptic loosening was 97.9% (CI: 96.5–99.4) for uncoated and 97.8% (CI: 96.3–99.4) for HA-coated cups. Adjusted HRs were 0.66 (CI 0.42–1.04) for the presence of HA coating during the first 10 years and 0.87 (CI 0.14–5.38) from year 10–13, compared with uncoated cups. When considering the endpoint cup revision for any reason, unadjusted 13-year survival was similar for uncoated (92.5% [CI: 90.1–94.9]) and HA-coated (94.7% [CI: 93.2–96.3]) cups. The risk of revision of any component due to infection was higher in THA with HA-coated cups than in THA with uncoated cups (adjusted HR 1.4 [CI 1.1–1.9]).

Conclusions: HA-coated cups have a similar risk of aseptic loosening as uncoated cups, thus the use of HA coating seems to not confer any added value in terms of implant stability. The risk of infection seemed higher in THA with use of HA-coated cups, an observation that must be investigated further.

Introduction

Hydroxyapatite (HA) coating of orthopaedic implants accelerates early bone ingrowth in experimental settings[1]. Several HA-coated uncemented cups were introduced in order to improve early implant stability and to increase long-term implant survival[2–4]. Due to its osteoconductive properties, HA has been suggested to improve both primary and secondary stability of orthopaedic implants, and this has been evaluated by radiostereometric analysis[5–7]. The use of HA coatings on uncemented

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arthroplasty implants has recently gained new momentum since HA is used as a carrier for antimicrobial agents[8,9].

Initial reports on HA-coated uncemented cups suggested better rotational stability and reduced incidence of radiolucent lines[5–7], with promising results after up to 10 years[10–12]. On the other hand, some randomized controlled studies fail to show beneficial effects of HA-coating on acetabular stability with up to 18 years follow-up[13–16]. Moreover, several publications on relatively small cohorts (up to 85 hips investigated) describe high failure rates of various cups coated with HA, which experimentally was explained by insufficient coating on grit-blasted surfaces[17–21]. Furthermore, some registry studies indicate an increased risk of aseptic loosening of HA-coated cups after primary total hip arthroplasty (THA) and a slightly higher risk of isolated liner revisions of HA-coated cups used in revision THA[22–24], a phenomenon possibly attributable to third-body wear or HA delamination[25,26].

The question whether HA coating is beneficial or not is thus highly relevant and controversial[27–29]. We therefore investigated long-term outcome of uncemented cups used with and without HA coating and in the Nordic countries during the last 18 years. Our primary outcome was cup revision due to aseptic loosening. Secondary endpoints were cup revision for any reason and revision of any component for any reason or due to infection.

Patients and methods

Q4 Sources of data and terminology

Our data were derived from the Nordic Arthroplasty Register Association (NARA) including the years 1995–2013. Data from the Danish, Finnish, Norwegian and Swedish arthroplasty registers have been continuously merged into a common NARA database[30,31]. In this study, the term "cup revision" was defined as an intervention where one or more components of the cup (shell, liner, or both) were removed or exchanged. Other types of re-operations where the implant was left *in situ* or where only the stem but not the cup was exchanged/removed were disregarded when the outcome was "cup revision". When the outcome was "revision of any component", all re-operations where a component was exchanged (either only cup, or only liner, only stem, only the femoral head, or a combination of any of these) were included. After applying exclusion criteria (see Section "Characteristics of the study population" and Fig. 1) all procedures were derived from the part of the database that was provided by Denmark, Norway and Sweden, whereas Finnish procedures had to be excluded due to missing information on important variables.

Statistics

Continuous data description was performed using means, medians and ranges. Estimation uncertainty was assessed by calculating 95% confidence intervals (CIs). Categorical data were cross-tabulated and proportions were investigated by the Chi-square test. Kaplan–Meier survival analysis was used to calculate cumulative unadjusted survival functions, with cup revision due to aseptic loosening as the primary endpoint, and cup revisions for any reason as secondary endpoint. Additional secondary endpoints were revision of any component for any reason or due to infection.

Multivariable Cox regression models were fitted in order to calculate crude and adjusted hazard ratios (HRs) with CI for the endpoints described above. The following covariates were included in the multivariable models: presence of HA coating, age at the time of primary THA (categorized into the four groups: <45, 45–64, 65–74, and 75 years and above, chosen in accordance with previous publications on related topics), gender, surgical approach, type of liner material (ultra-high molecular weight or highly cross-linked polyethylene), femoral head size, and type of stem fixation (cemented or uncemented).

Total observation time ranged up to 18 years, but since the number at risk was below 50 after 13 years the analysis was restricted to the first 13 years. Since cumulative survival curves for the endpoint cup revision due to aseptic loosening crossed after 10 years separate regression models were fitted up to 10 years and for the subsequent period from 10 to 13 years. For the other investigated endpoints unadjusted survival curves did not cross, and multivariable models were fitted for the entire observation period. When the scarcity of events in certain subgroups of a given covariate age inflated CIs this covariate was entered as a strata variable in our regression models. Log–log plots and Schoenfeld residuals indicated that the proportional-hazards assumption was fulfilled in all final models.

The analysis of both joints in bilaterally operated patients can lead to dependency issues, since both Kaplan–Meier survival analysis and Cox proportional hazards modelling are based on the assumption of independent observations[32,33]. Although inclusion of bilateral observations seems not to create dependency problems in large-size registry studies[34–36] we excluded the second operation in bilaterally operated cases (see Fig. 1).

The level of statistical significance was set at $P < 0.05$ in all analyses, and SPSS (version 23) and R (version 3.0.2) software together with the "rms" and "Epi" packages were used[37].

Characteristics of the study population

From 1995 to 2013 188,945 primary THA procedures using an uncemented cup were identified in the NARA database (Fig. 1). In order to reduce bias introduced by small numbers of cups we excluded procedures involving an uncemented cup that had been implanted less than 400 times in each country ($n = 20,387$ THA)[23,24]. In order to rigorously define the study population we also excluded all cases performed with other than metal-on-polyethylene articulations ($n = 111,593$) in order to avoid problems related to hard-on-hard bearings that could bias our findings due to inferior results of ceramic-on-ceramic or metal-on-metal articulations. We furthermore restricted the database to cups of the same design used with or without HA coating performed due to osteoarthritis, and excluded all other underlying diagnoses ($n = 12,051$). Furthermore, all procedures where information on HA coating of the cup component or on type of polyethylene liner was not available were excluded ($n = 14,943$). Finally, all cases where information on femoral head size was missing or head sizes other than the frequently used 28, 32 and 36 mm diameters had been recorded, were also excluded from the study ($n = 1,366$). That left a total number of 28,605 THA procedures involving three different uncemented cups (Trilogy® (Zimmer), $n = 20,049$; Pinnacle® (DePuy), $n = 4,463$; Exceed® (Biomet), $n = 4,093$; see Suppl. Table V).

Results

The group of uncoated cups was larger than the group of HA-coated cups. Uncoated cups were used more frequently than the HA-coated cups within the first 5 and the last 4 years of the observation period (1995–1999 and 2010–2013), but the proportions of uncoated and HA-coated cups did not differ statistically significantly for the remaining study period (2000–2009; Suppl. Table IX). 21,391 cups (74.8%) were combined with uncemented stems, resulting in uncemented THA, and 7,214 cups (25.2%) were combined with cemented stems, resulting in classical hybrid THA (Table I). Median follow-up for all procedures was 3.0

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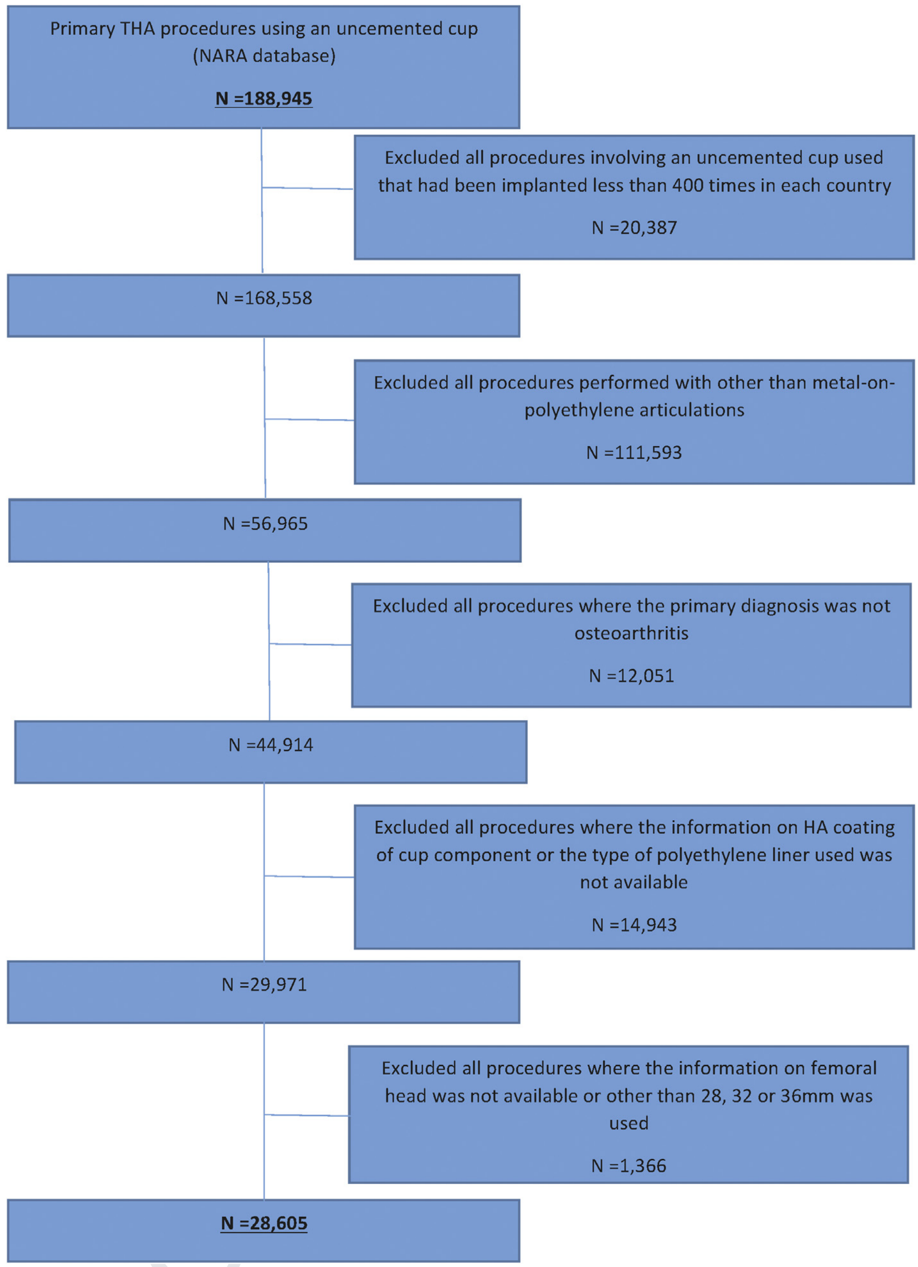

Fig. 1. Flowchart demonstrating the sequential exclusion of procedures not eligible for final analysis from the database.

(range: 0–18) years. The proportion of females was higher in the group of uncoated cups ($P < 0.001$), procedures performed in patients younger than 65 years were overrepresented in the group of HA-coated cups ($P < 0.001$), and the posterior surgical approach was more frequently used in the group of uncoated cups ($P < 0.001$, Table I). The distribution of sex and age groups within the participating countries is given in supplementary data (Suppl. Table V).

Risk of cup revision due to aseptic loosening

The unadjusted 13-year survival with the endpoint cup revision due to aseptic loosening was 97.9% (CI: 96.5–99.4) for uncoated cups and 97.8% (CI: 96.3–99.4) for HA-coated cups (Tables II and IV, Fig. 2). The adjusted risk of cup revision due to aseptic loosening did not differ between uncoated and HA-coated cups, with a HR of 0.66 (CI 0.42–1.04) for the presence of HA coating during the first 10 years, and a HR of 0.87 (CI 0.14–5.38) from year 10 to year 13 (Table II).

Additional analyses of the three cup types separately revealed similar results (Suppl. Table VI).

Risk of cup revision for any reason

The unadjusted 13-year survival with the endpoint cup revision due to any reason was similar for uncoated (92.5% [CI: 90.1–94.9]) and HA-coated (94.7% [CI: 93.2–96.3]) cups (Table II). The adjusted risk of cup revision due to any reason was lower for HA-coated cups, with an adjusted risk HR 0.8 (CI 0.7–1.0; $P = 0.04$; Table II). This effect was mainly due to a lower risk of dislocation in the group of HA-coated cups: 209 (1.2%) revisions due to dislocation were performed in THA with uncoated cups, and 70 (0.6%) for THA with HA-coated cups ($P < 0.001$). When surgical approach was added as

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Table I
Sex, age, stem fixation, type of liner material, type of surgical approach, femoral head size and cup type distribution by HA coating

	No HA (*n*)	(%)	HA (*n*)	(%)
Male	7414	42	5566	50
Female	10,053	58	5572	50
<45	192	1	402	4
45–64	5389	31	5662	51
65–74	7037	40	3512	31
75>	4849	28	1562	14
Uncemented	13,043	75	8348	75
Hybrid	4424	25	2790	25
Conventional PE	5075	29	2947	27
XLPE	12,392	71	8191	73
Posterior approach*	16,029	94	6544	60
Other approaches	989	6	4437	40
Head size 28 mm	5786	33	4317	39
Head size 32 mm	3896	22	4361	39
Head size 36 mm	7785	44	2460	22
Trilogy	11,752	67	8297	75
Pinnacle	2969	17	1494	13
Exceed	2746	16	1347	12
Sum	*17,467*	*100*	*11,138*	*100*

* Missing values on 606 cases.

a variable in the Cox regression model the adjusted risk of cup revision was found similar between the two groups (adjusted risk HR for HA coated cups: 0.9, CI 0.7–1.0; $P = 0.05$; Table III). Posterior surgical approach was found to be a statistical significant risk factor for revision due to any reason with an adjusted risk HR for posterior approach 1.5 (CI 1.2–1.9; $P < 0.001$; Table III).

Revision risk of any component

During the study period 1,094 (3.8%) revisions of any component had been performed. 240 (0.8%) THAs were revised due to aseptic loosening of either the cup or stem or both components, 349 (1.2%) revisions of any component were performed due to dislocation, and 200 (0.7%) were revised due to infection.

When separated by the presence or absence of HA coating, 13-year survival with the endpoint revision of any component for any reason was 87.4% (CI 84.5–90.4) for THA using uncoated cups and 90.7% (CI 88.6–92.7) for THA using HA-coated cups.

102 revisions of any component due to infection were performed in the HA-coated group and 98 revisions due to infection in the uncoated group (Suppl. Table VIII). 167 (83.5%) of all revisions due to infection were performed during the first 2 years after the primary THA. 13-year survival with the endpoint revision of any component due to infection was similar for THA using uncoated cups (98.3% [CI 97.3–99.3]) and THA using HA-coated cups (98.5% [CI 98.1–98.9]; $P < 0.001$). When adjusting for age, gender, and type of stem fixation (cemented or uncemented) we found that THA with HA-coated cups had a higher risk of revision of any component due to infection than THA with uncoated cups (adjusted risk HR: 1.4, CI 1.1–1.9; $P = 0.002$).

Table III
Relative risk (HR) of cup revision for any reason during the first 13 years

Endpoint: Any reason	Crude HR (95% CI)	Adjusted HR (95% CI)	*P* value
Coating			
−HA	1.0 (ref)	1.0 (ref)	
+HA	0.8 (0.7–0.9)	0.9 (0.7–1.0)	0.06
Polyethylene			
Highly cross linked	1.0 (ref)	1.0 (ref)	
Conventional	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.45
Stem fixation			
Uncemented	1.0 (ref)	1.0 (ref)	
Cemented	0.9 (0.8–1.1)	1.0 (0.8–1.2)	0.94
Surgical approach			
Other approaches	1.0 (ref)	1.0 (ref)	
Posterior approach	1.6 (1.3–2.0)	1.5 (1.2–1.9)	<0.001
Femoral head size*			
28 mm	1.0 (ref)	1.0 (ref)	
32 mm	1.1 (0.9–1.3)	1.1 (0.9–1.4)	0.39
36 mm	1.1 (0.9–1.4)	1.0 (0.8–1.3)	0.89

A Cox proportional hazards model was used to investigate the influence of HA coating adjusted for relevant covariates (age, gender, type of polyethylene liner, type of stem fixation, surgical approach and femoral head size) on the relative risk (HR) of cup revision (with 95% CIs) for any reason.
HR = Hazard ratio.

Table IV
Number at risk for HA coated and uncoated cups after 1, 3, 5, 7, 10 and 13 years in Kaplan–Meier survival analysis with HA coating as the independent factor and cup revision due to aseptic loosening as the endpoint

Endpoint: Aseptic loosening	Numbers at risk						
Years	0	1	3	5	7	10	13
Coating							
−HA	17,465	13,427	7958	5192	2943	295	138
+HA	11,138	9432	6106	3805	2499	793	82

Discussion

The presence of HA coating on uncemented cups used in primary THA performed due to osteoarthritis did not have a clinically relevant impact on the long-term risk of revision due to aseptic cup loosening. During the first 10 years the risk of cup revision due to aseptic loosening was marginally lower for HA-coated cups, but thereafter the survival curves crossed and survival of HA-coated cups was marginally worse. The risk of revision of any

Table II
10- and 13-year cup survival for aseptic loosening and relative risk (HR) of cup revision due to aseptic loosening during the first 10 years, and from year 10 to year 13. 13-year cup survival and HR of cup revision for any reason

Endpoint	10-year survival (95% CI)	13-year survival (95% CI)	Crude HR (95% CI) (0–10 years)	Adjusted HR (95% CI) (0–10 years)	Crude HR (95% CI) (10–13 years)	Adjusted HR (95% CI) (10–13 years)
Aseptic loosening						
−HA	98.9 (98.4–99.4)	97.9 (96.5–99.4)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
+HA	99.1 (98.7–99.6)	97.8 (96.3–99.4)	0.7 (0.4–1.0)	0.7 (0.4–1.0)	1.3 (0.2–7.2)	0.9 (0.1–5.4)
Any reason						
−HA		92.5 (90.1–94.9)			1.0 (ref)	1.0 (ref)
+HA		94.7 (93.2–96.3)			0.9* (0.7–0.9)	0.8* (0.7–1.0)

A Cox proportional hazards model was used to investigate the influence of HA coating adjusted for relevant covariates (age, gender, type of polyethylene liner, femoral head size and type of stem fixation) on the relative risk (HR) of cup revision (with 95% CIs) due to aseptic loosening or for any reason.
HR = Hazard ratio.
* Crude and adjusted HR was calculated for the entire observation time (0–13 years).

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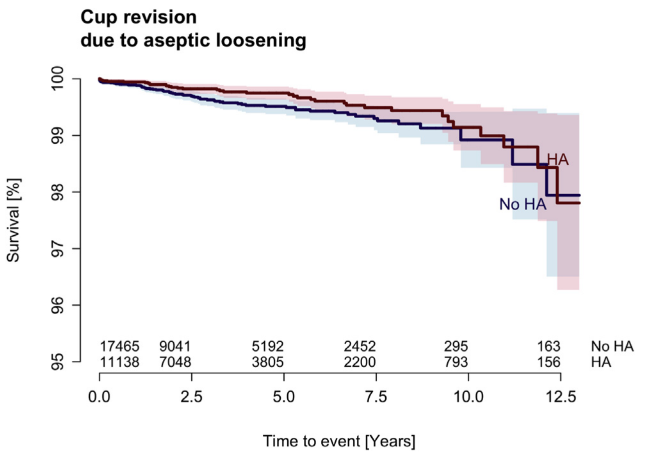

Fig. 2. Kaplan–Meier survival analysis with HA coating as the independent factor and cup revision due to aseptic loosening as the endpoint. Survival curves with 95% CI for the HA-coated cups (red) and for the uncoated stems (blue). Numbers at risk for each group along the x-axis.

component due to infection was higher in THA using HA-coated cups, an unexpected finding that has not been previously described.

Pro's and Con's of HA coating

Contrary to initial expectations showing reduced implant migration, subsequent investigations—both observational studies based on registry material and randomized controlled trials using radiostereometry—indicate no, minor positive or negative effects of HA coating on uncemented cup survival[7,15,23,24,38–40]. In the present study, we failed to see a clinically relevant difference in cup survival between HA-coated and uncoated cups when investigating the risk of aseptic loosening, which again challenges the contention that HA improves initial stability or bony ingrowth of uncemented acetabular cups. This conclusion is in agreement with a recent meta-analysis on the topic of HA coating of acetabular cups which also found no advantage of HA-coated over uncoated cups in terms of implant survival[41].

The question why HA does not improve cup survival cannot be answered on the basis of observational studies alone. Retrieval studies, however, indicate that HA particles derived from the coating can contribute to acceleration of third-body wear and osteolysis[25,42]. Resorption of HA and in some cases delamination of the coating has been shown in retrieval studies of HA-coated cups[43]. This may jeopardize the initially enhanced bone ingrowth and can contribute to adverse effects that result in polyethylene wear, osteolysis, and cup loosening.

The use of either conventional or highly cross-linked polyethylene (XLPE) is an important covariate to consider when comparing the risk of cup revision due to aseptic loosening, and liner type was therefore included as a covariate in our analyses (Table II). The combination of cups with different stem types could also distort our results due to differences in stem survival. The large number of different cup-and-stem combinations made a comprehensive analysis of the factor "stem brand" impossible, since the large number of degrees of freedom when entering individual stem types into Cox regression model resulted in meaningless estimates. As a proxy, the covariate "stem fixation" was therefore included in multivariable regression models, and we performed additional survival analyses stratified by the type of stem fixation. However, the type of stem fixation seemed not to confer any statistically significant effect on the investigated estimates (Tables II and III, Suppl. Table VIII).

In our material, the posterior approach dominated in the group of uncoated cups, and since the risk of dislocation is higher after the use the posterior approach[44,45] the unadjusted risk of revision for any reason was accordingly higher in uncoated cups. This increased risk of revision for any reason in uncoated cups was attenuated when the surgical approach was added as a covariate into a multivariable regression model with this endpoint. Another factor with a profound influence on the risk of dislocation and therefore on the risk of revision for any reason is femoral head size[43]. In our dataset, femoral head sizes were unevenly distributed between the two investigated groups of cups, but the covariate femoral head size did not statistically significantly affect the risk estimates for uncoated vs HA-coated cups (Table III).

Unexpectedly, the risk of revision of any component due to infection was higher in THA with HA-coated cups. The observation is novel, and we cannot exclude that uncontrolled confounders may contribute to this finding. We attempted to take the effects of cement-loaded antibiotics around cemented stems into account by adjusting for the type of stem fixation, but differences in the type, dose or duration of perioperative antibiotics—a variable not included in the NARA database—may be present and cannot be accounted for. Given the renewed interest in HA as a carrier of antimicrobial agents this finding indicates that further research on the ability of bacteria to adhere to HA and their ability to form biofilm on it is necessary. It may even be that bacterial adhesion to HA-coated surfaces is enhanced[46].

Strengths and weaknesses of the study

The strengths of this study are (1) its sample size, (2) the validity of the combined NARA dataset, and (3) the comparison of presence or absence of HA coating in three different cup designs.

- Previous studies suggest relatively small effects of HA coating on the risk of aseptic loosening, and a sample size such as ours was therefore needed to address this issue. Although this—at least to our knowledge—is the largest comparison of long-term survival in uncoated and HA-coated cups, we found only small and statistically insignificant differences in terms of the risk of revision due to aseptic loosening.
- The NARA dataset is based on the combined Danish, Norwegian, Swedish and Finnish hip arthroplasty registers that have all been repeatedly validated, and the completeness of data in the four countries ranges from 86% to 99%[47–52]. However, when we had applied all exclusion criteria mentioned in the methods section no cases from Finland were included in our analyses.
- A wide variety of cups with or without HA coating is available on the market, but comparisons of uncoated with HA-coated cups may be difficult since brands differ in many other parameters apart from their coating. We thus decided to only investigate cups that were available with or without HA coating, thus enabling direct comparisons of cup designs that were otherwise identical. A smaller, retrospective cohort study on cups that were identical apart from the presence or absence of HA coating was recently published, but with a much smaller sample size of $n = 183$[14].

Our study has several weaknesses. Although completeness and validity of the NARA database can be relied upon to a large extent, coding errors of variables such as implant characteristics and procedural details can occur. This is also true for information on HA coating and on femoral head size, leading to exclusion of 11,998 cases from the database (Fig. 1). This, of course, can create selection bias. Implant coding and identification may also differ between countries, but we attempted to minimize this potential source of error by reviewing the implant coding lists from each country and by contacting manufacturers and their representatives in the respective countries in order to reduce the risk of misclassification. The notion that HA coating could improve cup stability may have led surgeons to choose this implant rather than the porous coated version in situations where compromised bone contact was expected, introducing confounding by indication bias to the disadvantage of HA-coated cups. However, this bias could also have been inverted if porous surfaces (that tend to be rougher than HA-coated surfaces) were more frequently used in cases where primary stability was expected to be difficult to achieve. We attempted to address this issue by excluding all other diagnoses than osteoarthritis, since this eliminates a large number of cases with dysplastic or post-traumatic arthritis where bone stock is by definition compromised.

Furthermore, some hospitals may have had only one cup type available (either HA-coated or uncoated), and underperforming units may have used only one of these two options which opens up for the presence of performance bias. We investigated three different cup designs that were used either with or without HA coating in the Nordic countries, but we cannot exclude that HA coating on other cup designs than those studied may have beneficial effects on long-term stability and prosthesis survival. On the other hand, the investigated cup designs are widely used even outside the Nordic countries. One has to be cautious when generalizing our findings based on three cup types to other cup brands, but we believe that our findings do weaken the case for HA coating of uncemented acetabular cups. In our database, the Trilogy cup was by far the most frequently used cup, both with and without HA coating (Table I), and this implant had a follow-up of 18 years, which renders additional strength to our study. Moreover, the additional sensitivity analysis that included only the Trilogy cup resulted in risk estimates that were similar to those obtained from the main analyses of all three cup types (Suppl. Table IV).

Several other confounding factors cannot be analysed in an observational study that is based on arthroplasty registry data: For instance, medication with drugs such as bisphosphonates that are known to influence bone metabolism and that can increase the risk of atypical femoral fractures and medical comorbidities such as diabetes mellitus or obesity could all affect implant survival. This restriction also applies to the investigation of the risk of infection, where the type and dosage of systemic or local antibiotic prophylaxis (in cases where stems were fixed with antibiotic-loaded cement) are important confounders that we were unable to control for.

Conclusion

In conclusion, HA coating seems to confer no clinically relevant effect on the long-term survival of certain uncemented cups used in primary THA. We attained a slightly higher risk of revision of any component due to infection in THA using HA-coated cups, a finding that has to be investigated further. Based on these findings, the use of HA as a coating of cups seems not to add value in these devices.

Authors contribution

SL: Study design, database preparation, data analysis, manuscript drafting and editing; NPH: study design, data analysis, manuscript editing; JK, KTM, SO, GH, LIH, ABP: study design, final manuscript editing.

Q5 Conflict of interest

None of the authors declares any competing interests.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2017.08.001.

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